JAPANESE MACAQUE HERPESVIRUS NUCLEIC ACID AND POLYPEPTIDE SEQUENCES AND THEIR USE

STATEMENT OF GOVERNMENT SUPPORT

5   This disclosure was made with United States government support pursuant to grant RR00163 and CA75922 from the National Institutes of Health; the United States government has certain rights in the invention.

PRIORITY CLAIM

10   This is a continuation-in part of U.S. Application No. 10/276,524, filed November 13, 2002, which is a § 371 U.S. national stage of International Application No. PCT/US01/16274, filed May 17, 2001, which was published in English under PCT Article 21(2), and claims the benefit of U.S. Provisional Application No. 60/205,652 filed May 18, 2000. These applications are incorporated herein by reference.

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FIELD

This application relates to a Japanese macaque herpesvirus (JMHV), specifically to the nucleic acid sequence of the virus, open reading frames in this virus, and to amino acid sequences encoded by these sequences. Compositions and

20   methods are provided for the production of animal models useful in assessing the efficacy of drugs for the treatment or prevention of conditions associated with infection by the virus, such as multiple sclerosis.

BACKGROUND

25   An autoimmune disease is a condition that results from a pathological immune reaction against an individual's own tissues. Examples of autoimmune diseases, in which the immune system attacks otherwise healthy tissue include multiple sclerosis (MS), autoimmune uveitis, myasthenia gravis (MG), psoriasis, and rheumatoid arthritis (RA).

30   Multiple sclerosis (MS) is a chronic, neurological, autoimmune, demyelinating disease. MS can cause blurred vision, unilateral vision loss (optic neuritis), loss of balance, poor coordination, slurred speech, tremors, numbness,

extreme fatigue, changes in intellectual function (such as memory and concentration), muscular weakness, paresthesias, and blindness. Many subjects develop chronic progressive disabilities, but long periods of clinical stability may interrupt periods of deterioration. Neurological deficits may be permanent or

5   evanescent. In the United States there are about 250,000 to 400,000 persons with MS, and every week about 200 new cases are diagnosed. Worldwide, MS may affect 2.5 million individuals. Because it is not contagious, which would require U.S. physicians to report new cases, and because symptoms can be difficult to detect, the incidence of disease is only estimated and the actual number of persons

10   with MS could be much higher.

The pathology of MS is characterized by an abnormal immune response directed against the central nervous system. In particular, T-lymphocytes are activated against the myelin sheath of the central nervous system causing demyelination. In the demyelination process, myelin is destroyed and replaced by

15   scars of hardened "sclerotic" tissue which is known as plaque. These lesions appear in scattered locations throughout the brain, optic nerve, and spinal cord. Demyelination interferes with conduction of nerve impulses, which produces the symptoms of multiple sclerosis. Most patients recover clinically from individual bouts of demyelination, producing the classic remitting and exacerbating course of

20   the most common form of the disease known as relapsing-remitting multiple sclerosis.

Although the immune system plays an important role in the pathogenesis of MS, epidemiological data and the inflammatory nature of the disease suggests that a viral or bacterial infection may trigger the autoimmune attack against nerve cells in

25   genetically susceptible individuals. Many pathogens have been associated with MS, such as Epstein-Barr virus (EBV), Herpes simplex virus type 1 (HSV-1), Human herpesvirus-6 (HHV-6) and *Chlamydia pneumoniae*. While there is no solid evidence that supports any one infectious agent as the causative agent of MS, experimental models suggest that the disease may result from one of three different

30   mechanisms including: i) immunologic response against bacterial/viral antigens in the central nervous system (CNS), resulting in demyelination; ii) an infectious agent in CNS that releases myelin antigens that initiate an autoimmune reaction against myelin, a concept referred to as "epitope spread"; and iii) a virus or bacteria that

contains antigens with significant homology with myelin antigens and thus elicit an immunologic response against the infectious agent and the myelin antigens, a process referred to as "molecular mimicry."

5   There is a need to develop animal models of multiple sclerosis. Specifically, these animal models can be used to evaluate agents that can be used to treat this disease. Any treatment that could delay the progression or recurrence of the disease would be enormously beneficial to people who have this disease, by reducing neurological impairment and disability.

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SUMMARY

Japanese macaques can harbor a virus related to Rhesus macaque rhadinovirus (RRV), called Japanese macaque herpesvirus (JMHV). An isolated virus is disclosed herein (Japanese macaque herpesvirus, JMHV) as deposited with 15   ATCC as Deposit Accession No. PTA-1884, deposited May 18, 2000, as are viral particles including this virus and host cells infected with this virus. The entire nucleic acids sequence of this virus is provided herein. Also disclosed are the nucleic acid sequences of unique open reading frames, and the polypeptide sequences encoded by these open reading frames. Pharmaceutical compositions are 20   also disclosed that include the viral nucleic acid, a polypeptide encoded by the viral nucleic acid, an antibody that binds the JMHV polypeptide, or a polynucleotide encoding at least one JMHV polypeptide.

In one embodiment, a method is provided for testing the efficacy of a drug in the treatment of a condition associated with infection with JMHV. In one example, 25   the method includes administering the drug to a non-human primate infected with JMHV; and observing the non-human primate to determine if the drug prevents or reduces the presentation of one or more symptoms associated with JMHV infection.

In a further embodiment, a method is provided for detecting the presence of JMHV or a related virus in a biological specimen, by amplifying by polymerase 30   chain reaction a JMHV nucleic acid sequence, or by using hybridization technology, if such sequence is present in the sample.

A method is also provided for detecting the presence of JMHV in a biological specimen, including contacting the biological specimen with an antibody

that binds to a JMHV polypeptide, and detecting binding of the antibody to the biological specimen or a component thereof. Binding of the antibody to the biological specimen indicates the presence of JMHV.

Kits are provided that include an antibody that binds to a JMHV polypeptide or an oligonucleotide that hybridizes to a JMHV nucleic acid sequence.

The foregoing and other objects, features, and advantages of the disclosure will become more apparent from the following detailed description of several examples which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic diagram of an ORF map of the JMHV genome. Map of the JMHV genome showing the ORFs that are homologous to JMHV, RRV, Kaposi's sarcoma-associated herpesvirus (KSHV) and Herpesvirus saimiri (HVS) (light gray arrows), JMHV and RRV (gray arrows), JMHV, RRV and KSHV (white arrows), JMHV unknown (black arrows), and JMHV unique (dark gray arrows). JMHV putative genes are numbered according to Table 1 from JM1 to JM171.

SEQUENCE LISTING

The nucleic and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases, and three letter code for amino acids, as defined in 37 C.F.R. 1.822. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included by any reference to the displayed strand. In the accompanying sequence listing:

SEQ ID NO: 1 is the nucleic acid sequences of JMHV.

SEQ ID NOs: 2-172 are the amino acid sequences of polypeptides encoded by JMHV.

DETAILED DESCRIPTION

I.   Abbreviations

CPE: Cytopathic effects

EAE: Autoimmune encephalomyelitis

JME: Japanese macaque encephalomyelitis

JMHV: Japanese macaque herpesvirus

MS: Multiple sclerosis

ORF: Open reading frame

PCR: Polymerase chain reaction

RRV: Rhesus macaque rhadinovirus

TEM: Transmission electron microscopy

II.   Terms

Unless otherwise noted, technical terms are used according to conventional usage. Definitions of common terms in molecular biology may be found in Benjamin Lewin, *Genes V*, published by Oxford University Press, 1994 (ISBN 0-19-854287-9); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); and Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive Desk Reference*, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8).

In order to facilitate review of the various embodiments of this disclosure, the following explanations of specific terms are provided.

Amplification of a nucleic acid molecule (for example, a DNA or RNA molecule): A technique that increases the number of copies of a nucleic acid molecule in a specimen. An example of amplification is the polymerase chain reaction in which a biological sample collected from a subject is contacted with a pair of oligonucleotide primers, under conditions that allow for the hybridization of the primers to a nucleic acid template in the sample. The primers are extended under suitable conditions, dissociated from the template, and then re-annealed, extended, and dissociated to amplify the number of copies of the nucleic acid. The product of amplification may be characterized by electrophoresis, restriction endonuclease cleavage patterns, oligonucleotide hybridization or ligation, and/or nucleic acid

sequencing using standard techniques. Other examples of amplification include strand displacement amplification, as disclosed in U.S. Patent No. 5,744,311; transcription-free isothermal amplification, as disclosed in U.S. Patent No. 6,033,881; repair chain reaction amplification, as disclosed in WO 90/01069; ligase

5   chain reaction amplification, as disclosed in EP 0320308; gap filling ligase chain reaction amplification, as disclosed in U.S. Patent No. 5,427,930; and NASBA™ RNA transcription-free amplification, as disclosed in U.S. Patent No. 6,025,134.

Animal: Living multicellular vertebrate organisms, a category which includes, for example, humans, non-human primates, mammals, and birds.

10   **Antibody:** Immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, for instance, molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen.

A naturally occurring antibody (for example, IgG, IgM, IgD) includes four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected

15   by disulfide bonds. However, it has been shown that the antigen-binding function of an antibody can be performed by fragments of a naturally occurring antibody. Thus, these antigen-binding fragments are also intended to be designated by the term "antibody." Specific, non-limiting examples of binding fragments encompassed within the term antibody include (i) an Fab fragment consisting of the V_L, V_H, CL,

20   and CH1 domains; (ii) an Fd fragment consisting of the V_H and CH1 domains; (iii) an Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (iv) a dAb fragment (Ward et al., *Nature* 341:544-546, 1989) which consists of a V_H domain; (v) an isolated complimentarity determining region (CDR); and (vi) an F(ab')$_2$ fragment, a bivalent fragment comprising two Fab fragments

25   linked by a disulfide bridge at the hinge region.

Immunoglobulins and certain variants thereof are known and many have been prepared in recombinant cell culture (for example, see U.S. Patent No. 4,745,055; U.S. Patent No. 4,444,487; WO 88/03565; EP 0256654; EP 0120694; EP 0125023; Faoulkner et al., *Nature* 298:286, 1982; Morrison, *J. Immunol.*

30   123:793, 1979; Morrison et al., *Ann Rev. Immunol* 2:239, 1984).

Autoimmune disorder: A disorder in which the immune system produces an immune response (e.g. a B cell or a T cell response) against an endogenous antigen, with consequent injury to tissues.

Cell: A plant, animal, insect, bacterial, or fungal cell.

Conservative variants: "Conservative" amino acid substitutions are those substitutions that do not substantially affect or decrease an activity or antigenicity of a JMHV polypeptide. Specific, non-limiting examples of a conservative substitution include the following examples:

Original Residue	Conservative Substitutions
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
His	Asn; Gln
Ile	Leu, Val
Leu	Ile; Val
Lys	Arg; Gln; Glu
Met	Leu; Ile
Phe	Met; Leu; Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile; Leu

The term conservative variation also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid, provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide. Non-conservative substitutions are those that reduce an activity or antigenicity.

Degenerate variant: A polynucleotide encoding a JMHV polypeptide that includes a sequence that is degenerate as a result of the genetic code. There are 20 natural amino acids, most of which are specified by more than one codon. Therefore, all degenerate nucleotide sequences are included in the disclosure as long as the amino acid sequence of the JMHV polypeptide encoded by the nucleotide sequence is unchanged.

Expression Control Sequences: Nucleic acid sequences that control and regulate the expression of a nucleic acid sequence, such as a heterologous nucleic

acid sequence, to which it is operably linked. Expression control sequences are operably linked to a nucleic acid sequence when the expression control sequences control and regulate the transcription and, as appropriate, translation of the nucleic acid sequence. Thus expression control sequences can include appropriate

5 promoters, enhancers, transcription terminators, polyA signals, a start codon (for instance, ATG) in front of a protein-encoding polynucleotide sequence, splicing signal for introns, maintenance of the correct reading frame of that gene to permit proper translation of mRNA, and stop codons. The term "control sequences" is intended to include, at a minimum, components whose presence can influence

10 expression, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. Expression control sequences can include a promoter.

A promoter is a minimal sequence sufficient to direct transcription of a nucleic acid. Promoters may be cell-type specific or tissue specific. A promoter

15 includes necessary nucleic acid sequences near the start site of transcription, such as, in the case of a polymerase II type promoter, a TATA element. A promoter also optionally includes distal enhancer or repressor elements which can be located as much as several thousand base pairs from the start site of transcription. Both constitutive and inducible promoters are included (see for example, Bitter et al.,

20 *Methods in Enzymology* 153:516-544, 1987).

For example, when cloning in bacterial systems, inducible promoters such as pL of bacteriophage lambda, plac, ptrp, ptac (ptrp-lac-hybrid promoter) and the like may be used. In one embodiment, when cloning in mammalian cell systems, promoters derived from the genome of mammalian cells (for example,

25 metallothionein promoter) or from mammalian viruses (for example, the retrovirus long terminal repeat; the adenovirus late promoter; the vaccinia virus 7.5K promoter) can be used. Promoters produced by recombinant DNA or synthetic techniques may also be used to provide for transcription of the nucleic acid sequences. A polynucleotide can be inserted into an expression vector that contains

30 a promoter sequence which facilitates the efficient transcription of the inserted genetic sequence of the host. The expression vector typically contains an origin of replication, a promoter, as well as specific nucleic acid sequences that allow

phenotypic selection of the transformed cells. In one embodiment, the promoter is a cytomegalovirus promoter.

Herpesvirus: Viruses that include large (genomes up to 235kbp DNA) that are generally complex viruses such that the virus encodes about 35 virion proteins. Herpesviruses encode a variety of enzymes involved in nucleic acid metabolism, DNA synthesis and protein processing (protein kinase).

The herpesvirus particle is complex, and includes a core that has a toroidal shape, with the large DNA genome would around a proteinaceous core. The complex capsid surrounds the core. Outside the capsid is the tegument, a protein-filled region which appears amorphous in electron micrographs. On the outside of the particle is the envelope, which contains numerous glycoproteins.

Herpesvirus genomes can have a unique long (UL) and a unique short (US) region, bounded by inverted repeats. The repeats allow rearrangements of the unique regions and Herpesvirus genomes exist as a mixture of four isomers. Herpesvirus genomes also contain multiple repeated sequences. The JMHV genome, however, has a unique long region bound by inverted repeat, which is consistent for gamma-herpesvirues.

Homologs: Two nucleotide or amino acid sequences that share a common ancestral sequence and diverged when a species carrying that ancestral sequence split into two species. Homologs frequently show a substantial degree of sequence identity.

Immuno-compromised: Lacking a normal immune response. Immuno-compromised refers to a condition in which some or all of an animal's immune system is inoperative, leaving the animal with an increased susceptibility to infection or disease. An animal may be rendered immuno-compromised by a biological agent such as, in the case of non-human primates, Simian Immunodeficiency Virus (SIV). Many strains of SIV have been isolated and characterized; any SIV strain that produces an immuno-compromised state can be used in the present disclosure including, but not limited to, for example, SIVmac239 (Kestler et al., *Science* 248:1109-12, 1990), SIVmac251 (Daniels et al., *Science* 228:1201-4, 1985), SIVdeltaB670 (Murphy-Corb et al., *Nature* 321:435, 1986) and SIVmne (Benveniste et al., *J. Virol.* 62:2091-101, 1988). In addition, hybrid SIV/HIV chimeras as known in the field can be employed, as can HIV-2. Simian type D retroviruses (SRVs),

which cause an AIDS-like disease in rhesus monkeys, can alternatively be used to immuno-compromise the animals in place of SIV. These viral agents are administered to the animal using conventional means, such as intravenous or intramuscular injection, or oral, intrarectal or intravaginal inoculation (also see

5   Example 24). Either intact viral particles or viral DNA may be administered. As known in the field, plasmid constructs containing the entire SIV genome are infectious when inoculated into animals and so may be employed in place of purified viral DNA.

Alternatively, an animal may be rendered immuno-compromised by

10   administration of agents that target the immune system, including but not limited to anti-CD3 antibody (CD3 being the T cell receptor) either alone or conjugated with a toxic moiety, or immunosuppressive compounds including prednisone, azathioprine, cyclosporine A, and cyclophosphamide. Where an immunosuppressive compound such as cyclosporine is employed, an allogenic stimulus (such as a blood

15   transfusion) may be administered with the subsequent administration of RRV to activate infection.

Alternatively, other methods of rendering an animal immuno-compromised may be used, including radiation treatment and surgical intervention.

Immune response: A response of a cell of the immune system, such as a B

20   cell, T cell, or monocyte, to a stimulus. In one embodiment, the response is specific for a particular antigen (an "antigen-specific response"). The response can also be a non-specific response (not targeted specifically to salivary polypeptides) such as production of lymphokines. In one embodiment, an immune response is a T cell response, such as a CD4+ response or a CD8+ response. In another embodiment,

25   the response is a Th1 (a subset of helper T cells) response. In yet another embodiment, the response is a B cell response, and results in the production of specific antibodies.

Isolated: An "isolated" biological component (such as a nucleic acid, peptide or protein) has been substantially separated, produced apart from, or purified

30   away from other biological components in the cell of the organism in which the component naturally occurs, i.e., other chromosomal and extrachromosomal DNA and RNA, and proteins. Nucleic acids, peptides and proteins which have been "isolated" thus include nucleic acids and proteins purified by standard purification

methods. The term also embraces nucleic acids, peptides and proteins prepared by recombinant expression in a host cell as well as chemically synthesized nucleic acids.

Japanese Macaque Herpesvirus (JMHV): A virus having the virological,
5   immunological or pathological characteristics of Japanese macaque herpesvirus (e.g. JMHV 17792). JMHV causes the symptoms of MS in Japanese macaque monkeys which are infected with the virus. In particular examples, the JMHV has at least 85% (for example at least 90%, 95% or 98%) sequence identity to the JMHV deposited with the virus deposited as ATCC Accession No. PTA-1884. In other
10   examples, the JMHV has at least 90%, 91%, 92%, 93%, 94%, 95%, or 98% homology with an RRV (e.g. ATCC VR-2901). Without being bound by theory, the JMHV may be derived from an RRV (see the experimental examples).

JMHV 17792: Japanese macaque herpesvirus isolate 17792. A Budapest Treaty deposit of JMHV 17792 was made with the American Type Culture
15   Collection (ATCC), Manassas, Virginia, on May 18, 2001. This virus may be grown on primary Japanese macaque fibroblasts, using standard virological techniques. Alternatively, it may be grown on commercially available macaque cell lines. Infection of a non-human primate with JMHV 17792 can be accomplished using any standard method, including intravenous injection. In one embodiment,
20   infection is achieved using 10^6 plaque forming units of JMHV 17792.

Label: A detectable compound or composition that is conjugated directly or indirectly to another molecule to facilitate detection of that molecule. Specific, non-limiting examples of labels include fluorescent tags, enzymatic linkages, and radioactive isotopes.

25   **Multiple Sclerosis:** A chronic, progressive disease of the central nervous system. Currently, the exact cause of the disease is unknown and there is no cure. Multiple sclerosis refers to multiple areas of patchy scarring, or plaques, that result from demyelination (destruction of myelin, a fatty insulation covering the nerve fibers). When the myelin sheath is destroyed during the MS disease process, signals
30   transmitted throughout the CNS are slowed or disrupted. In many cases, the body may compensate for the loss of myelin by increasing the density of the sodium channels so that action potentials can continue to be carried, in spite of loss of

myelin. The nerves also retain the capacity to remyelinate. Unfortunately, the disease process often outpaces these corrective actions.

The symptoms, severity, and course of MS vary widely depending partly on the sites of the plaques and the extent of the demyelination. Experts generally group

5   multiple sclerosis into four types: relapsing-remitting, primary-progressive, secondary-progressive, and progressive-relapsing MS. Relapsing-remitting multiple sclerosis generally occurs in younger people and is the most common form of MS. Symptoms flare up for several days and then go into remission over the next four to eight weeks. The latter three forms (primary-progressive, secondary-progressive,

10   and progressive-relapsing MS) generally fall under the category of chronic-progressive MS. In chronic-progressive MS the symptoms of the disease continue to worsen slowly without remission. About 20% of multiple sclerosis patients (usually those patients whose first symptoms occur after age 45) have the chronic-progressive form of MS without first developing relapsing-remitting MS. Chronic-

15   progressive MS may lead to serious speech problems and paralysis, and generally the symptoms continue to worsen over time.

Multiple sclerosis is defined as an autoimmune disease; that is, the body's immune system is damaged by genetic or environmental factors or both, causing it to attack its own tissues. In the case of MS, these tissues are the myelin covering the

20   nerve fibers in the brain.

A symptom of MS is any physical characteristic associated with the disease process. For example, the first symptom of MS is often optic neuritis, the inflammation of the optic nerve. Vision, usually in one eye, becomes unclear or doubled, and there may be a shimmering effect. Pain or nystagmus, involuntary

25   jerking or movement of the eye, may also occur. In 20% of people with this condition, MS develops within two years; in 45% to 80% it develops within 15 years. Other early symptoms of multiple sclerosis include fatigue, heaviness or clumsiness in the arms and legs, tingling sensations, and poor coordination. Another indication of MS is a reaction known as Llermitte's sign, whereby bending the neck

30   produces an electrical sensation that runs down the back and into the legs.

As the disease develops over months or even years, other symptoms may include spasticity, imbalance, tremors, incontinence, constipation, sexual dysfunction, hearing loss, vertigo, facial pain, and difficulties in swallowing.

Problems in speech may occur because of difficulty in controlling the quality of the voice and articulating words. About half of patients display changes in mental function, including problems in concentration and problem solving. In about 10% of cases, there is severe mental dysfunction which resembles dementia. One of the

5   primary symptoms of MS is spasticity, which is characterized by weakness, loss of dexterity, and the inability to control specific movements.

Myelin: A coating of nerve cells (neurons) made from layers of cell membranes that are produced in the brain and spinal cord by specialized cells called oligodendrocytes. Myelin coats lie in segments along the axons, the long filaments

10   that carry electric impulses away from a nerve cell. The segments are separated from each other by tiny clusters called nodes of Ranvier, which house channels for sodium ions. These sodium ions are important for boosting the electrical charge required to pass signals from one nerve to another.

Non-human primate: Simian primates including chimpanzees, orangutans,

15   baboons, and macaques. Any non-human primate may be used to produce a KSHV-disease animal model or a JMHV-disease animal model by the methods disclosed herein. Thus, in addition to the rhesus macaque and Japanese macaque models described in detail below, pigtail and cynomologus macaques and baboons may also be used to produce KSHV-disease or JMHV-disease animal models by the methods

20   disclosed herein.

Oligonucleotide: A linear polynucleotide sequence of up to about 200 nucleotide bases in length, for example a polynucleotide (such as DNA or RNA) which is at least 6 nucleotides, for example at least 15, 25, 50, 100 or even 200 nucleotides long.

25   **Operably linked:** A first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA

30   sequences are contiguous and, where necessary to join two protein coding regions, in the same reading frame.

ORF: Open reading frame. Contains a series of nucleotide triplets (codons) coding for amino acids without any termination codons. These sequences are usually translatable into protein.

PCR: Polymerase chain reaction. Describes a technique in which cycles of 5   denaturation, annealing with primer, and then extension with DNA polymerase are used to amplify the number of copies of a target DNA sequence.

Polypeptide: A polymer in which the monomers are amino acid residues that are joined together through amide bonds. When the amino acids are alpha-amino acids, either the L-optical isomer or the D-optical isomer can be used, the L-10   isomers being preferred. The terms "polypeptide" or "protein" as used herein is intended to encompass any amino acid sequence and include modified sequences such as glycoproteins. The term "polypeptide" is specifically intended to cover naturally occurring proteins, as well as those that are recombinantly or synthetically produced.

15   The term "fragment" refers to a portion of a polypeptide that is at least 8, 10, 15, 20 or 25 amino acids in length. The term "functional fragments of a polypeptide" refers to all fragments of a polypeptide that retain an activity of the polypeptide (e.g., the binding of an antigen). Biologically functional fragments, for example, can vary in size from a polypeptide fragment as small as an epitope 20   capable of binding an antibody molecule to a large polypeptide capable of participating in the characteristic induction or programming of phenotypic changes within a cell. The term "soluble" refers to a form of a polypeptide that is not inserted into a cell membrane.

Polypeptide modifications: JMHV polypeptides include synthetic 25   embodiments of polypeptides described herein. In addition, analogs (non-peptide organic molecules), derivatives (chemically functionalized peptide molecules obtained starting with the disclosed polypeptide sequences) and variants (homologs) of these proteins can be utilized in the methods described herein. Each polypeptide of the disclosure is comprised of a sequence of amino acids, which may be either L-30   and/or D- amino acids, naturally occurring and otherwise.

Polypeptides may be modified by a variety of chemical techniques to produce derivatives having essentially the same activity as the unmodified polypeptides, and optionally having other desirable properties. For example,

carboxylic acid groups of the protein, whether carboxyl-terminal or side chain, may
be provided in the form of a salt of a pharmaceutically-acceptable cation or
esterified to form a C_1-C_{16} ester, or converted to an amide of formula NR_1R_2
wherein R_1 and R_2 are each independently H or C_1-C_{16} alkyl, or combined to form a

5   heterocyclic ring, such as a 5- or 6-membered ring. Amino groups of the peptide,
whether amino-terminal or side chain, may be in the form of a pharmaceutically-
acceptable acid addition salt, such as the HCl, HBr, acetic, benzoic, toluene sulfonic,
maleic, tartaric, and other organic salts, or may be modified to C_1-C_{16} alkyl or
dialkyl amino or further converted to an amide.

10   Hydroxyl groups of the peptide side chains may be converted to C_1-C_{16}
alkoxy or to a C_1-C_{16} ester using well-recognized techniques. Phenyl and phenolic
rings of the peptide side chains may be substituted with one or more halogen atoms,
such as fluorine, chlorine, bromine, or iodine, or with C_1-C_{16} alkyl, C_1-C_{16} alkoxy,
carboxylic acids and esters thereof, or amides of such carboxylic acids. Methylene

15   groups of the peptide side chains can be extended to homologous C_2-C_4 alkylenes.
Thiols can be protected with any one of a number of well-recognized protecting
groups, such as acetamide groups. Those skilled in the art will also recognize
methods for introducing cyclic structures into the peptides of this disclosure to select
and provide conformational constraints to the structure that result in enhanced

20   stability.

Peptidomimetic and organomimetic embodiments are envisioned, whereby
the three-dimensional arrangement of the chemical constituents of such peptido- and
organomimetics mimic the three-dimensional arrangement of the peptide backbone
and component amino acid side chains, resulting in such peptido- and

25   organomimetics of a *L. longipalpis* polypeptide having measurable or enhanced
ability to generate an immune response. For computer modeling applications, a
pharmacophore is an idealized, three-dimensional definition of the structural
requirements for biological activity. Peptido- and organomimetics can be designed
to fit each pharmacophore with current computer modeling software (using

30   computer assisted drug design or CADD). See Walters, "Computer-Assisted
Modeling of Drugs," Klegerman & Groves (eds.), 1993, *Pharmaceutical
Biotechnology*, Interpharm Press: Buffalo Grove, IL, pp. 165-174 and *Principles of*

Pharmacology Munson (ed.) 1995, Ch. 102, for descriptions of techniques used in CADD. Also included are mimetics prepared using such techniques.

Pharmaceutically acceptable carriers: The pharmaceutically acceptable carriers useful in this disclosure include conventional carriers. *Remington's*

5 *Pharmaceutical Sciences*, by E. W. Martin, Mack Publishing Co., Easton, PA, 15th Edition (1975), describes compositions and formulations suitable for pharmaceutical delivery of the viruses, nucleic acids and/or proteins herein disclosed.

In general, the nature of the carrier will depend on the particular mode of administration being employed. For instance, parenteral formulations usually

10 comprise injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol, ethanol, combinations thereof, or the like, as a vehicle. The carrier and composition can be sterile, and the formulation suits the mode of administration. For solid compositions (e.g., powder, pill, tablet, or capsule forms),

15 conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, sodium saccharine, cellulose, magnesium carbonate, or magnesium stearate. In addition to biologically-neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and

20 pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as

25 triglycerides.

Probes and primers: Nucleic acid probes and primers may readily be prepared based on the amino acid sequences provided by this disclosure. A probe is an isolated nucleic acid attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, fluorescent molecules,

30 chemiluminescent molecules, and enzymes. In other embodiments, labels include co-factors, enzyme substrates; and haptens.

Methods for labeling and guidance in the choice of labels appropriate for various purposes are discussed, e.g., in Sambrook et al., in *Molecular Cloning: A*

Laboratory Manual, Cold Spring (1989) and Ausubel et al., in *Current Protocols in Molecular Biology,* Greene Publishing Associates and Wiley-Intersciences (1987).

Primers are short nucleic acids, such as DNA oligonucleotides 10 nucleotides or more in length. Primers may be annealed to a complementary target DNA strand by nucleic acid hybridization to form a hybrid between the primer and the target DNA strand, and then extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR) or other nucleic-acid amplification methods known in the art.

Methods for preparing and using probes and primers are described, for example, in Sambrook et al. (*Molecular Cloning: A Laboratory Manual,* 2nd ed., vol. 1-3, Cold Spring Harbor, New York. 1989); Ausubel et al. (*Current Protocols in Molecular Biology,* Greene Publ. Assoc. & Wiley-Intersciences. 1987) and Innis et al. (*PCR Protocols, A Guide to Methods and Applications,* 1990, Innis et al. (eds.), 21-27, Academic Press, Inc., San Diego, California). PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, © 1991, Whitehead Institute for Biomedical Research, Cambridge, MA).

Probes and primers as used in the present disclosure typically comprise at least 15 contiguous nucleotides of the RRV genome sequence (SEQ ID NO: 1), or 15 contiguous nucleotides of a JMHV sequence. One of skill in the art will appreciate that the specificity of a particular probe or primer increases with its length. Thus, for example, a primer comprising 20 consecutive nucleotides will anneal to a target with a higher specificity than a corresponding primer of only 15 nucleotides. Thus, in order to obtain greater specificity, probes and primers may be selected that comprise 20, 25, 30, 35, 40, 50 or more consecutive nucleotides. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 30, 40, 50, 60, 70, 80, 90, 100, or 150 consecutive nucleotides of the disclosed nucleic acid sequences.

Alternatively, such probes and primers may comprise at least 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, or 150 consecutive nucleotides that share a defined level of sequence identity with the disclosed RRV or JMHV sequence, for instance, at least a 60%, 70%, 80%, 90%, 95% or 98% sequence identity. Alternatively, such probes

and primers may be nucleotide molecules which hybridize under wash conditions of 70°C and about 0.2 x SSC for 1 hour, or alternatively under less stringent conditions of 65°C, 60°C, or 55°C with from about 0.2 to 2 x SSC (with, for instance, about 0.1% SDS) for 1 hour with a portion of the JMHV sequence.

Protein Purification: The JMHV polypeptides disclosed herein can be purified by any of the means known in the art. See, e.g., *Guide to Protein Purification*, ed. Deutscher, *Meth. Enzymol.* 185, Academic Press, San Diego, 1990; and Scopes, *Protein Purification: Principles and Practice*, Springer Verlag, New York, 1982. Substantial purification denotes purification from other proteins or cellular components. A substantially purified protein is at least 60%, 70%, 80%, 90%, 95% or 98% pure. Thus, in one specific, non-limiting example, a substantially purified protein is 90% free of other proteins or cellular components.

Purified (Isolated): The term purified or isloated does not require absolute purity; rather, it is intended as a relative term. Thus, for example, a purified peptide preparation is one in which the peptide or protein is more enriched than the peptide or protein is in its natural environment within a cell. Preferably, a preparation is purified such that the protein or peptide represents at least 50% of the total peptide or protein content of the preparation.

Recombinant: A recombinant nucleic acid is one that has a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques.

RRV 17577: Rhesus macaque rhadinovirus RRV isolate 17577. A Budapest Treaty deposit of RRV 17577 was made with the American Type Culture Collection, Manassas, Virginia, on March 12, 1998, and has been accorded ATCC Accession No. VR-2601. This virus may be grown on primary rhesus fibroblasts, as described below (see Examples 1 and 14), using standard virological techniques. Alternatively, it may be grown on commercially available rhesus cell lines, including those available from ATCC, such as ATCC CRL-6306 and ATCC CL-160. Infection of a non-human primate with RRV 17577 may be accomplished using any standard method, including intravenous injection (see Examples 13, 23

and 24). Typically, infection is achieved by intravenous injection of around 10^6 plaque forming units (PFUs) of RRV 17577.

Rhesus Macaque Rhadinovirus (RRV): A virus having the virological and immunological characteristics of RRV 17577, which causes Kaposi's sarcoma-like disease and lymphoma in infected immunocompromised rhesus monkeys (see published PCT Application No. WO 00/28040 and U.S. Patent Application No. 09/831,000, filed May 2, 2001, which are both incorporated by reference herein).

Sequence Identity: The similarity between two nucleic acid sequences, or two amino acid sequences, is expressed in terms of the similarity between the sequences, otherwise referred to as sequence identity. Sequence identity is frequently measured in terms of percentage identity (or similarity or homology); the higher the percentage, the more similar the two sequences are. Homologs or orthologs of nucleic acid or amino acid sequences will possess a relatively high degree of sequence identity when aligned using standard methods. This homology will be more significant when the orthologous proteins or nucleic acids are derived from species which are more closely related (e.g., human and chimpanzee sequences), compared to species more distantly related (e.g., human and *C. elegans* sequences). Typically, orthologs are at least 50% identical at the nucleotide level and at least 50% identical at the amino acid level when comparing human orthologous sequences.

Methods of alignment of sequences for comparison are well known. Various programs and alignment algorithms are described in: Smith & Waterman, *Adv. Appl. Math.* 2:482, 1981; Needleman & Wunsch, *J. Mol. Biol.* 48:443, 1970; Pearson & Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444, 1988; Higgins & Sharp, Gene, 73:237-44, 1988; Higgins & Sharp, *CABIOS* 5:151-3, 1989; Corpet et al., *Nuc. Acids Res.* 16:10881-90, 1988; Huang et al., *Computer Appls. Biosci.* 8:155-65, 1992; and Pearson et al., *Meth. Mol. Bio.* 24:307-31, 1994. Altschul et al., *J. Mol. Biol.* 215:403-10, 1990, presents a detailed consideration of sequence alignment methods and homology calculations.

The NCBI Basic Local Alignment Search Tool (BLAST) (Altschul et al., *J. Mol. Biol.* 215:403-10, 1990) is available from several sources, including the National Center for Biotechnology Information (NCBI, Bethesda, MD) and on the Internet, for use in connection with the sequence analysis programs blastp, blastn,

blastx, tblastn and tblastx. Each of these sources also provides a description of how to determine sequence identity using this program.

Homologous sequences are typically characterized by possession of at least 60%, 70%, 75%, 80%, 90%, 95% or at least 98% sequence identity counted over the

5   full length alignment with a sequence using the NCBI Blast 2.0, gapped blastp set to default parameters. Queries searched with the blastn program are filtered with DUST (Hancock and Armstrong, *Comput. Appl. Biosci.* 10:67-70, 1994). It will be appreciated that these sequence identity ranges are provided for guidance only; it is entirely possible that strongly significant homologs could be obtained that fall

10   outside of the ranges provided.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences, due to the degeneracy of the genetic code. It is understood that changes in nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode

15   substantially the same protein.

One indication that two nucleic acid sequences are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid.

An alternative indication that two nucleic acid molecules are closely related

20   is that the two molecules hybridize to each other under stringent conditions, as described under "specific hybridization."

Homologs of the disclosed RRV or JMHV nucleic acids typically possess at least 50% sequence identity counted over the length of one of the nucleic acids (the reference nucleic acid) using the NCBI Blast 2.0.6, gapped blastn set to default

25   parameters. Nucleic acids showing substantial similarity when assessed by this method may show, for example, at least 50%, 60%, 70%, 80%, 90%, 95% or even 98% or greater sequence identity. When less than the entire sequence is being compared for sequence identity, substantially similar nucleotide sequences will typically possess at least 70% sequence identity over short windows of 30-90

30   nucleic acids, and may possess sequence identities of at least 80%, 90%, 95% or 98% or greater.

Homologs of the disclosed RRV or JMHV proteins typically possess at least 50% sequence identity counted over full-length alignment with the amino acid

sequence of RRV using the NCBI Blast 2.0, gapped blastp set to default parameters. For comparisons of amino acid sequences of greater than about 30 amino acids, the Blast 2 sequences function is employed using the default BLOSUM62 matrix set to default parameters, (gap existence cost of 11, and a per residue gap cost of 1). When aligning short peptides (fewer than around 30 amino acids), the alignment should be performed using the Blast 2 sequences function, employing the PAM30 matrix set to default parameters (open gap 9, extension gap 1 penalties). Proteins with even greater similarity to the reference sequence will show increasing percentage identities when assessed by this method, such as at least 50%, at least 55%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity. When less than the entire sequence is being compared for sequence identity, homologs will typically possess at least 70% sequence identity over short windows of 10-20 amino acids, and may possess sequence identities of at least 75%, at least 85% or at least 90%, at least 95% or 98% depending on their similarity to the reference sequence.

When comparing degrees of sequence identity between similar proteins, the degree of identity will be equal to or less than that the degree of similarity, due to the fact the similarity takes into account conservative amino acid substitutions. So, for instance, the degree of sequence identity between to substantially similar proteins may be at least 50%, 55%, 65%, 75%, 85%, 95%, 98% or more.

One of ordinary skill in the art will appreciate that these sequence identity ranges are provided for guidance only; it is entirely possible that strongly significant homologs could be obtained that fall outside of the ranges provided. The present disclosure provides not only the peptide homologs that are described above, but also nucleic acid molecules that encode such homologs.

An alternative indication that two nucleic acid molecules are closely related is that the two molecules hybridize to each other under stringent conditions. In nucleic acid hybridization reactions, the conditions used to achieve a particular level of stringency will vary, depending on the nature of the nucleic acids being hybridized. For example, the length, degree of complementarity, nucleotide sequence composition (*e.g.*, GC v. AT content), and nucleic acid type (*e.g.*, RNA v. DNA) of the hybridizing regions of the nucleic acids can be considered in

selecting hybridization conditions. An additional consideration is whether one of the nucleic acids is immobilized, for example, on a filter.

Specific hybridization: Specific hybridization refers to the binding, duplexing, or hybridizing of a molecule only or substantially only to a particular

5   nucleotide sequence when that sequence is present in a complex mixture (e.g. total cellular DNA or RNA). Specific hybridization may also occur under conditions of varying stringency.

A specific, non-limiting example of progressively higher stringency conditions is as follows: 2 x SSC/0.1% SDS at about room temperature

10   (hybridization conditions); 0.2 x SSC/0.1% SDS at about room temperature (low stringency conditions); 0.2 x SSC/0.1% SDS at about 42°C (moderate stringency conditions); and 0.1 x SSC at about 68°C (high stringency conditions). One of skill in the art can readily determine variations on these conditions (for example, *Molecular Cloning: A Laboratory Manual*, 2nd ed., vol. 1-3, ed. Sambrook et al.,

15   Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989). The hydridization conditions can be carried out over 2 to 16 hours. Washing can be carried out using only one of the above conditions, for example, high stringency conditions, or each of the conditions can be used, for example, for 10-15 minutes each, in the order listed above, repeating any or all of the steps listed. However,

20   as mentioned above, optimal conditions will vary, depending on the particular hybridization reaction involved, and can be determined empirically.

Specific binding agent: An agent that binds substantially only to a defined target. As used herein, the term "JMHV peptide specific binding agent" includes anti-JMHV peptide antibodies and other agents that bind substantially only to the

25   JMH peptide. The antibodies may be monoclonal or polyclonal antibodies that are specific for a JMHV peptide, as well as immunologically effective portions ("fragments") thereof.

In one embodiment, the antibodies are monoclonal antibodies (or immunologically effective portions thereof) and may also be humanized monoclonal

30   antibodies (or immunologically effective portions thereof). Immunologically effective portions of monoclonal antibodies include Fab, Fab', F(ab')$_2$, Fabc and Fv portions (for a review, see Better and Horowitz, *Methods. Enzymol.* 178:476-96,

1989). Anti-inhibitory peptide antibodies may also be produced using standard procedures described in a number of texts, including *Antibodies, A Laboratory Manual* by Harlow and Lane, Cold Spring Harbor Laboratory (1988).

Methods of making humanized monoclonal antibodies are well known, and

5   include those described in U.S. Patent No. 5,585,089; U.S. Patent No. 5,565,332; U.S. Patent No. 5,225,539; U.S. Patent No. 5,693,761; U.S. Patent No. 5,693,762; U.S. Patent No. 5,585,089; and U.S. Patent No. 5,530,101 and references cited therein. Similarly, methods of making and using immunologically effective portions of monoclonal antibodies, also referred to as antibody fragments, are well known

10   and include those described in Better and Horowitz, *Meth. Enzymol.* 178:176-496, 1989; Better et al., 1990, Better and Horowitz, 1990, *Advances in Gene technology: The Molecular Biology of Immune Disease & the Immune Response* (ICSU Short Reports); Glockshuber et al., *Biochemistry* 29:1362-7, 1990; and U.S. Patent No. 5,648,237; U.S. Patent No. 4,946,778 and U.S. Patent No. 5,455,030, and references

15   cited therein.

The determination that a particular agent binds substantially only to a JMHV peptide may readily be made by using or adapting routine procedures. One suitable *in vitro* assay makes use of the Western blotting procedure (described in many standard texts, including *Antibodies, A Laboratory Manual* by Harlow and Lane).

20   Western blotting may be used to determine that a given JMHV peptide binding agent, binds substantially only to the specific JMHV protein.

Supernatant: The culture medium in which a cell is grown. The culture medium includes material from the cell. If the cell is infected with a virus, the supernatant can include viral particles.

25   **Subject:** This term includes both human and non-human subjects. Similarly, the term "patient" includes both human and veterinary subjects. In one embodiment, the subject has multiple sclerosis.

Symptom and sign: Any subjective evidence of disease or of a subject's condition, i.e., such evidence as perceived by the subject; a noticeable change in a

30   subject's condition indicative of some bodily or mental state. A "sign" is any abnormality indicative of disease, discoverable on examination or assessment of a subject. A sign is generally an objective indication of disease. Signs include, but

are not limited to any measurable parameters such as tests for immunological status
or the presence of lesions in a subject with multiple sclerosis.

     Therapeutically Effective Amount: A dose sufficient to prevent
advancement, or to cause regression of the disease, or which is capable of reducing

5   symptoms caused by the disease, such as multiple sclerosis.

     Transduced: A transduced cell is a cell into which has been introduced a
nucleic acid molecule by molecular biology techniques. As used herein, the term
transduction encompasses all techniques by which a nucleic acid molecule might be
introduced into such a cell, including transfection with viral vectors, transformation

10   with plasmid vectors, and introduction of naked DNA by electroporation,
lipofection, and particle gun acceleration.

     Transgenic Cell: Transformed cells which contain foreign, non-native
DNA.

     Variants of Amino Acid and Nucleic Acid Sequences: The production of

15   RRV or JMHV proteins can be accomplished in a variety of ways (for example see
Examples 17, 21 and 25). DNA sequences which encode the protein, or a fragment
of the protein, can be engineered such that they allow the protein to be expressed in
eukaryotic cells, bacteria, insects, and/or plants. In order to accomplish this
expression, the DNA sequence can be altered and operably linked to other regulatory

20   sequences. The final product, which contains the regulatory sequences and the
therapeutic protein, is referred to as a vector. This vector can then be introduced
into the eukaryotic cells, bacteria, insect, and/or plant. Once inside the cell the
vector allows the protein to be produced.

     One of ordinary skill in the art will appreciate that the DNA can be altered in

25   numerous ways without affecting the biological activity of the encoded protein. For
example, PCR may be used to produce variations in the DNA sequence which
encodes JMHV proteins. Such variants may be variants that are optimized for codon
preference in a host cell that is to be used to express the protein, or other sequence
changes that facilitate expression.

30   Two types of cDNA sequence variant may be produced. In the first type, the
variation in the cDNA sequence is not manifested as a change in the amino acid
sequence of the encoded polypeptide. These silent variations are simply a reflection
of the degeneracy of the genetic code. In the second type, the cDNA sequence

variation does result in a change in the amino acid sequence of the encoded protein. In such cases, the variant cDNA sequence produces a variant polypeptide sequence. In order to preserve the functional and immunologic identity of the encoded polypeptide, it is preferred that any such amino acid substitutions are conservative.

5   Conservative substitutions replace one amino acid with another amino acid that has some homology in size, hydrophobicity, etc. Such substitutions generally are conservative when it is desired to finely modulate the characteristics of the protein. For example, conservative substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or

10   helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

Examples of amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative substitutions include: Ser for Ala; Lys for Arg; Gln or His for Asn; Glu for Asp; Ser for Cys; Asn for Gln; Asp

15   for Glu; Pro for Gly; Asn or Gln for His; Leu or Val for Ile; Ile or Val for Leu; Arg or Gln for Lys; Leu or Ile for Met; Met, Leu or Tyr for Phe; Thr for Ser; Ser for Thr; Tyr for Trp; Trp or Phe for Tyr; and Ile or Leu for Val.

The substitutions which in general are expected to produce the greatest changes in protein properties will be non-conservative, for instance changes in

20   which (a) a hydrophilic residue, e.g., seryl or threonyl, is substituted for (or by) a hydrophobic residue, e.g., leucyl, isoleucyl, phenylalanyl, valyl or alanyl; (b) a cysteine or proline is substituted for (or by) any other residue; (c) a residue having an electropositive side chain, e.g., lysyl, arginyl, or histadyl, is substituted for (or by) an electronegative residue, e.g., glutamyl or aspartyl; or (d) a residue having a bulky

25   side chain, e.g., phenylalanine, is substituted for (or by) one not having a side chain, e.g., glycine.

Variations in the DNA sequence that result in amino acid changes, whether conservative or not, should be minimized in order to preserve the functional and immunologic identity of the encoded protein. The immunologic identity of the

30   protein may be assessed by determining whether it is recognized by an antibody to an RRV (or JMHV) protein; a variant that is recognized by such an antibody is immunologically conserved. Any DNA sequence variant will preferably introduce no more than 20, and preferably fewer than 10 amino acid substitutions into the

encoded polypeptide. Variant amino acid sequences can, for example, be 80%, 90%, 95% or even 98% identical to the native amino acid sequence.

Vector: A nucleic acid molecule as introduced into a host cell, thereby producing a transformed host cell. A vector may include nucleic acid sequences that permit it to replicate in the host cell, such as an origin of replication. A vector may also include one or more selectable marker genes and other genetic elements known in the art.

Virion: A complete viral particle including envelope, capsid (if any), and nucleic acid elements.

The present disclosure utilizes standard laboratory practices for the cloning, manipulation and sequencing of nucleic acids, purification and analysis of proteins and other molecular biological and biochemical techniques, unless otherwise stipulated. Such techniques are explained in detail in standard laboratory manuals such as Sambrook et al. (*Molecular Cloning: A Laboratory Manual*, 2nd ed., vol. 1-3, Cold Spring Harbor, New York, 1989) and Ausubel et al. (*Current Protocols in Molecular Biology*, Greene Publ. Assoc. & Wiley-Intersciences, 1987).

Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. It is further to be understood that all base sizes or amino acid sizes, and all molecular weight or molecular mass values, given for nucleic acids or polypeptides are approximate, and are provided for description. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The term "comprises" means "includes." All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including explanations of terms, will

control. In addition, the materials, methods, and examples are illustrative only and
not intended to be limiting.

Polynucleotides and Polypeptides

5   The sequence of a JMHV is disclosed herein (see SEQ ID NO: 1).
Homologous nucleic acid sequences including an nucleic acid sequence at least
about 90%, 95%, 98%, or 99% identical to the nucleic acid sequence as set forth in
SEQ ID NO: 1 are also disclosed herein. Polynucleotides encoding a JMHV
polypeptide (encoded by an open reading frame, or ORF) are also provided, and are
10   termed JMHV polynucleotides. These polynucleotides include DNA, cDNA and
RNA sequences which encode a JMHV polypeptide, or encode a polypeptide at least
about 85%, at least about 90%, at least about 95%, at least about 98%, or at least
about 99% homologous to the JMHV ORF (see Table 3). Specific, non-limiting
examples of a JMHV nucleic acid encoding a ORF are nucleic acid 21845 to nucleic
15   acid 22120 of SEQ ID NO: 1 (JMHV25), nucleic acid 22363 to nucleic acid 22701
of SEQ ID NO: 1 (JMHV26), nucleic acid 33254 to nucleic acid 33553 of SEQ ID
NO: 1 (JMHV39), nucleic acid 35301 to nucleic acid 35687 of SEQ ID NO: 1
(JMVH41), nucleic acid 40188 to nucleic acid 40439 of SEQ ID NO: 1 (JMHV48),
nucleic acid 45836 to nucleic acid 46195 of SEQ ID NO: 1 (JMHV54), nucleic acid
20   47768 to nucleic acid 48136 of SEQ ID NO: 1 (JM57), nucleic acid 57325 to nucleic
acid 57573 of SEQ ID NO: 1 (JM71), nucleic acid 62823 to nucleic acid 63086 of
SEQ ID NO: 1 (JM76), nucleic acid 65629 to nucleic acid 65880 of SEQ ID NO: 1
(JM80), nucleic acid 67920 to nucleic acid 68594 of SEQ ID NO: 1 (JM85), nucleic
acid to nucleic acid of SEQ ID NO: 1 (JM87), nucleic acid 70328 to nucleic acid
25   70606 of SEQ ID NO: 1 (JM88), nucleic acid 75447 to nucleic acid 75722 of SEQ
ID NO: 1 (JM95), nucleic acid 105581 to nucleic acid 106003 of SEQ ID NO: 1
(JM132), nucleic acid 117501 to nucleic acid 118265 of SEQ ID NO: 1 (JM152),
nucleic acid to nucleic acid of SEQ ID NO: 1 (JM159), nucleic acid to nucleic acid
of SEQ ID NO: 1 (JM166), and nucleic acid to nucleic acid of SEQ ID NO: 1
30   (JM167).

It is understood that all polynucleotides encoding a JMHV polypeptide are
also included herein, as long as they encode a polypeptide with the recognized
activity, such as the binding to an antibody that recognizes the JMHV polypeptide.

The JMHV polynucleotides include sequences that are degenerate as a result of the genetic code. There are 20 natural amino acids, most of which are specified by more than one codon. Therefore, all degenerate nucleotide sequences are included as long as the amino acid sequence of the JMHV polypeptide encoded by the nucleotide

5   sequence is functionally unchanged.

The JMHV polynucleotides include a recombinant DNA which is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule (e.g., a cDNA) independent of other sequences. The nucleotides can be

10   ribonucleotides, deoxyribonucleotides, or modified forms of either nucleotide. The term includes single and double forms of DNA. Also included are fragments of the above-described nucleic acid sequences that are at least 15 bases in length, which is sufficient to permit the fragment to selectively hybridize to DNA that encodes the disclosed JMHV polypeptide (such as a polynucleotide that is encoded by SEQ ID

15   NO: 1) under physiological conditions. These nucleic acids can be used as probes or primers for the identification of viral nucleic acid. The term "selectively hybridize" refers to hybridization under moderately or highly stringent conditions, which excludes non-related nucleotide sequences. The JMHV polynucleotide sequence disclosed herein include, but are not limited to, nucleic acid 21845 to nucleic acid

20   22120 of SEQ ID NO: 1 (JMHV25), nucleic acid 22363 to nucleic acid 22701 of SEQ ID NO: 1 (JMHV26), nucleic acid 33254 to nucleic acid 33553 of SEQ ID NO: 1 (JMHV39), nucleic acid 35301 to nucleic acid 35687 of SEQ ID NO: 1 (JMVH41), nucleic acid 40188 to nucleic acid 40439 of SEQ ID NO: 1 (JMHV48), nucleic acid 45836 to nucleic acid 46195 of SEQ ID NO: 1 (JMHV54), nucleic acid

25   47768 to nucleic acid 48136 of SEQ ID NO: 1 (JM57), nucleic acid 57325 to nucleic acid 57573 of SEQ ID NO: 1 (JM71), nucleic acid 62823 to nucleic acid 63086 of SEQ ID NO: 1 (JM76), nucleic acid 65629 to nucleic acid 65880 of SEQ ID NO: 1 (J(M80), nucleic acid 67920 to nucleic acid 68594 of SEQ ID NO: 1 (JM85), nucleic acid to nucleic acid of SEQ ID NO: 1 (JM87), nucleic acid 70328 to nucleic acid

30   70606 of SEQ ID NO: 1 (JM88), nucleic acid 75447 to nucleic acid 75722 of SEQ ID NO: 1 (JM95), nucleic acid 105581 to nucleic acid 106003 of SEQ ID NO: 1 (JM132), nucleic acid 117501 to nucleic acid 118265 of SEQ ID NO: 1 (JM152) , nucleic acid to nucleic acid of SEQ ID NO: 1 (JM159), nucleic acid to nucleic acid

of SEQ ID NO: 1 (JM166), and nucleic acid to nucleic acid of SEQ ID NO: 1 (JM167).

The JMHV polypeptides of this disclosure include polypeptides encoded by all of the open reading frames disclosed herein. Polypeptides least 85%, at least about 90%, at least about 95%, at least about 98%, or at least about 99% homologous to the JMHV ORF (see Table 3) are also encompassed by this disclosure. In one embodiment, these polypeptides retain a function of the ORF. The polypeptides also include amino acid sequences including at most one, at most two, at most three, at most four, at most five or at most ten conservative substitutions of the JMHV polypeptide. Fusion proteins are also contemplated that include a heterologous amino acid sequence chemically linked to a JMHV polypeptide. Exemplary fusion proteins include short amino acid sequence tags (such as six histidine residues) as well a fusion of other proteins (such as c-myc or green fluorescent protein fusions). Epitopes of the ORFs, that retain the ability to bind an antibody or to bind the major histocompatibility complex (MHC), and can be used to induce an immune response, are also encompassed by this disclosure. Specific examples of JMHV polypeptides are provided as SEQ ID NOs: 2-171.

DNA sequences encoding any JMHV polypeptide can be expressed *in vitro* by DNA transfer into a suitable host cell. The cell may be prokaryotic or eukaryotic. The term also includes any progeny of the subject host cell. It is understood that all progeny may not be identical to the parental cell since there may be mutations that occur during replication. Methods of stable transfer, meaning that the foreign DNA is continuously maintained in the host, are known in the art.

Polynucleotide sequences encoding an open reading frame of JMHV can be operatively linked to expression control sequences. An expression control sequence operatively linked to a coding sequence is ligated such that expression of the coding sequence is achieved under conditions compatible with the expression control sequences. The expression control sequences include, but are not limited to appropriate promoters, enhancers, transcription terminators, a start codon (i.e., ATG) in front of a protein-encoding gene, splicing signal for introns, maintenance of the correct reading frame of that gene to permit proper translation of mRNA, and stop codons.

The polynucleotide sequences encoding a JMHV ORF may be inserted into an expression vector including, but not limited to a plasmid, virus or other vehicle that can be manipulated to allow insertion or incorporation of sequences and can be expressed in either prokaryotes or eukaryotes. Hosts can include microbial, yeast,

5   insect and mammalian organisms. Methods of expressing DNA sequences having eukaryotic or viral sequences in prokaryotes are well known in the art. Biologically functional viral and plasmid DNA vectors capable of expression and replication in a host are known in the art.

Transformation of a host cell with recombinant DNA may be carried out by

10   conventional techniques as are well known to those skilled in the art. Where the host is prokaryotic, such as *E. coli*, competent cells which are capable of DNA uptake can be prepared from cells harvested after exponential growth phase and subsequently treated by the $CaCl_2$ method using procedures well known in the art. Alternatively, $MgCl_2$ or RbCl can be used. Transformation can also be performed

15   after forming a protoplast of the host cell if desired, or by electroporation.

When the host is a eukaryote, such methods of transfection of DNA as calcium phosphate coprecipitates, conventional mechanical procedures such as microinjection, electroporation, insertion of a plasmid encased in liposomes, or virus vectors may be used. Eukaryotic cells can also be cotransformed with JMHV

20   polynucleotide sequences, and a second foreign DNA molecule encoding a selectable phenotype, such as the herpes simplex thymidine kinase gene. Another method is to use a eukaryotic viral vector, such as simian virus 40 (SV40) or bovine papilloma virus, to transiently infect or transform eukaryotic cells and express the protein (see for example, *Eukaryotic Viral Vectors*, Cold Spring Harbor Laboratory,

25   Gluzman ed., 1982).

Isolation and purification of recombinantly expressed polypeptide may be carried out by conventional means including preparative chromatography and immunological separations. The peptides can be chemically synthesized by any of a number of manual or automated methods of synthesis known in the art. For

30   example, solid phase peptide synthesis (SPPS) is carried out on a 0.25 millimole (mmole) scale using an Applied Biosystems Model 431A Peptide Synthesizer and using 9-fluorenylmethyloxycarbonyl (Fmoc) amino-terminus protection, coupling with dicyclohexylcarbodiimide/ hydroxybenzotriazole or 2-(1H-benzo-triazol-1-yl)-

1,1,3,3-tetramethyluronium hexafluorophosphate/ hydroxybenzotriazole (HBTU/HOBT), and using p-hydroxymethylphenoxymethylpolystyrene (HMP) or Sasrin resin for carboxyl-terminus acids or Rink amide resin for carboxyl-terminus amides.

5   Fmoc-derivatized amino acids are prepared from the appropriate precursor amino acids by tritylation and triphenylmethanol in trifluoroacetic acid, followed by Fmoc derivitization as described by Atherton et al. (*Solid Phase Peptide Synthesis*, IRL Press: Oxford, 1989).

          Sasrin resin-bound peptides are cleaved using a solution of 1% TFA in

10   dichloromethane to yield the protected peptide. Where appropriate, protected peptide precursors are cyclized between the amino- and carboxyl-termini by reaction of the amino-terminal free amine and carboxyl-terminal free acid using diphenylphosphorylazide in nascent peptides wherein the amino acid sidechains are protected.

15   HMP or Rink amide resin-bound products are routinely cleaved and protected sidechain-containing cyclized peptides deprotected using a solution comprised of trifluoroacetic acid (TFA), optionally also comprising water, thioanisole, and ethanedithiol, in ratios of 100 : 5 : 5 : 2.5, for 0.5 - 3 hours at room temperature.

20   Crude peptides are purified by preparative high pressure liquid chromatography (HPLC), for example using a Waters Delta-Pak C18 column and gradient elution with 0.1% TFA in water modified with acetonitrile. After column elution, acetonitrile is evaporated from the eluted fractions, which are then lyophilized. The identity of each product so produced and purified may be

25   confirmed by fast atom bombardment mass spectroscopy (FABMS) or electrospray mass spectroscopy (ESMS).

30   **Antibodies**

          A JMHV polypeptide or a fragment or conservative variant thereof can be used to produce antibodies which are immunoreactive or bind to an epitope of the JMHV polypeptide. Polyclonal antibodies, antibodies which consist essentially of

pooled monoclonal antibodies with different epitopic specificities, as well as distinct monoclonal antibody preparations are included.

The preparation of polyclonal antibodies is well-known to those skilled in the art. See, for example, Green et al., "Production of Polyclonal Antisera," in

5   *Immunochemical Protocols* pages 1-5, Manson, ed., Humana Press 1992; Coligan et al., "Production of Polyclonal Antisera in Rabbits, Rats, Mice and Hamsters," in: *Current Protocols in Immunology*, section 2.4.1, 1992.

The preparation of monoclonal antibodies likewise is conventional. See, for example, Kohler & Milstein, *Nature* 256:495, 1975; Coligan et al., sections

10   2.5.1-2.6.7; and Harlow et al., in: *Antibodies: a Laboratory Manual*, page 726, Cold Spring Harbor Pub., 1988. Briefly, monoclonal antibodies can be obtained by injecting mice with a composition comprising an antigen, verifying the presence of antibody production by removing a serum sample, removing the spleen to obtain B lymphocytes, fusing the B lymphocytes with myeloma cells to produce hybridomas,

15   cloning the hybridomas, selecting positive clones that produce antibodies to the antigen, and isolating the antibodies from the hybridoma cultures. Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange

20   chromatography. See, e.g., Coligan et al., sections 2.7.1-2.7.12 and sections 2.9.1-2.9.3; Barnes et al., "Purification of Immunoglobulin G (IgG)," in: *Methods in Molecular Biology*, Vol. 10, pages 79-104, Humana Press, 1992.

Methods of *in vitro* and *in vivo* multiplication of monoclonal antibodies are well known to those skilled in the art. Multiplication *in vitro* may be carried out in

25   suitable culture media such as Dulbecco's Modified Eagle Medium or RPMI 1640 medium, optionally supplemented by a mammalian serum such as fetal calf serum or trace elements and growth-sustaining supplements such as normal mouse peritoneal exudate cells, spleen cells, thymocytes or bone marrow macrophages. Production *in vitro* provides relatively pure antibody preparations and allows scale-up to yield

30   large amounts of the desired antibodies. Large-scale hybridoma cultivation can be carried out by homogenous suspension culture in an airlift reactor, in a continuous stirrer reactor, or in immobilized or entrapped cell culture. Multiplication *in vivo* may be carried out by injecting cell clones into mammals histocompatible with the

parent cells, e.g., syngeneic mice, to cause growth of antibody-producing tumors. Optionally, the animals are primed with a hydrocarbon, especially oils such as pristane (tetramethylpentadecane) prior to injection. After one to three weeks, the desired monoclonal antibody is recovered from the body fluid of the animal.

5   Antibodies can also be derived from subhuman primate antibody. General techniques for raising therapeutically useful antibodies in baboons can be found, for example, in WO 91/11465, 1991, and Losman et al., *Int. J. Cancer* 46:310, 1990.

Alternatively, an antibody that specifically binds a JMHV polypeptide can be derived from a humanized monoclonal antibody. Humanized monoclonal antibodies

10   are produced by transferring mouse complementarity determining regions from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, and then substituting human residues in the framework regions of the murine counterparts. The use of antibody components derived from humanized monoclonal antibodies obviates potential problems associated with the

15   immunogenicity of murine constant regions. General techniques for cloning murine immunoglobulin variable domains are described, for example, by Orlandi et al., *Proc. Nat'l Acad. Sci. U.S.A.* 86:3833, 1989. Techniques for producing humanized monoclonal antibodies are described, for example, by Jones et al., *Nature* 321:522, 1986; Riechmann et al., *Nature* 332:323, 1988; Verhoeyen et al., *Science* 239:1534,

20   1988; Carter et al., *Proc. Nat'l Acad. Sci. U.S.A.* 89:4285, 1992; Sandhu, *Crit. Rev. Biotech.*12:437, 1992; and Singer et al., *J. Immunol.*150:2844, 1993.

Antibodies can be derived from human antibody fragments isolated from a combinatorial immunoglobulin library. See, for example, Barbas et al., in: *Methods: a Companion to Methods in Enzymology*, Vol. 2, page 119, 1991; Winter et al., *Ann.*

25   *Rev. Immunol.*12:433, 1994. Cloning and expression vectors that are useful for producing a human immunoglobulin phage library can be obtained, for example, from STRATAGENE Cloning Systems (La Jolla, CA).

In addition, antibodies can be derived from a human monoclonal antibody. Such antibodies are obtained from transgenic mice that have been "engineered" to

30   produce specific human antibodies in response to antigenic challenge. In this technique, elements of the human heavy and light chain loci are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy and light chain loci. The transgenic mice can

synthesize human antibodies specific for human antigens, and the mice can be used to produce human antibody-secreting hybridomas. Methods for obtaining human antibodies from transgenic mice are described by Green et al., *Nature Genet.* 7:13, 1994; Lonberg et al., *Nature* 368:856, 1994; and Taylor et al., *Int. Immunol.*6:579,

5   1994.

Antibodies include intact molecules as well as fragments thereof, such as Fab, F(ab')$_2$, and Fv which are capable of binding the epitopic determinant. These antibody fragments retain some ability to selectively bind with their antigen or receptor and are defined as follows:

10   (1)   Fab, the fragment which contains a monovalent antigen-binding fragment of an antibody molecule, can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain;

(2)   Fab', the fragment of an antibody molecule can be obtained by

15   treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain; two Fab' fragments are obtained per antibody molecule;

(3)   (Fab')$_2$, the fragment of the antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction; F(ab')$_2$ is a

20   dimer of two Fab' fragments held together by two disulfide bonds;

(4)   Fv, defined as a genetically engineered fragment containing the variable region of the light chain and the variable region of the heavy chain expressed as two chains; and

(5)   Single chain antibody (SCA), defined as a genetically engineered

25   molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule.

Methods of making these fragments are known in the art. (See for example, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor

30   Laboratory, New York, 1988). An epitope is any antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or

sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics.

Antibody fragments can be prepared by proteolytic hydrolysis of the antibody or by expression in *E. coli* of DNA encoding the fragment. Antibody
5   fragments can be obtained by pepsin or papain digestion of whole antibodies by conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment denoted F(ab')$_2$. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of
10 disulfide linkages, to produce 3.5S Fab' monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two monovalent Fab' fragments and an Fc fragment directly (see U.S. Patent No. 4,036,945 and U.S. Patent No. 4,331,647, and references contained therein; Nisonhoff et al., *Arch. Biochem. Biophys.*89:230, 1960; Porter, *Biochem. J.* 73:119, 1959; Edelman et al., *Methods in Enzymology*,
15 Vol. 1, page 422, Academic Press, 1967; and Coligan et al. at sections 2.8.1-2.8.10 and 2.10.1-2.10.4).

Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the
20 fragments bind to the antigen that is recognized by the intact antibody.

For example, Fv fragments comprise an association of V_H and V_L chains. This association may be noncovalent (Inbar et al., *Proc. Nat'l Acad. Sci. U.S.A.* 69:2659, 1972). Alternatively, the variable chains can be linked by an intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde.
25 See, e.g., Sandhu, *supra*. Preferably, the Fv fragments comprise V_H and V_L chains connected by a peptide linker. These single-chain antigen binding proteins (sFv) are prepared by constructing a structural gene comprising DNA sequences encoding the V_H and V_L domains connected by an oligonucleotide. The structural gene is inserted into an expression vector, which is subsequently introduced into a host cell such as
30 *E. coli*. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing sFvs are known in the art (see Whitlow et al., *Methods: a Companion to Methods in Enzymology*,

Vol. 2, page 97, 1991; Bird et al., *Science* 242:423, 1988; U.S. Patent No. 4,946,778; Pack et al., *Bio/Technology* 11:1271, 1993; and Sandhu, *supra)*.

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition
5   units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells (Larrick et al., *Methods: a Companion to Methods in Enzymology*, Vol. 2, page 106, 1991).

10   Antibodies can be prepared using an intact polypeptide or fragments containing small peptides of interest as the immunizing antigen. The polypeptide or a peptide used to immunize an animal can be derived from substantially purified polypeptide produced in host cells, *in vitro* translated cDNA, or chemical synthesis which can be conjugated to a carrier protein, if desired. Such commonly used
15   carriers which are chemically coupled to the peptide include keyhole limpet hemocyanin (KLH), thyroglobulin, bovine serum albumin (BSA), and tetanus toxoid. The coupled peptide is then used to immunize the animal (e.g., a mouse, a rat, or a rabbit).

Polyclonal or monoclonal antibodies can be further purified, for example, by
20   binding to and elution from a matrix to which the polypeptide or a peptide to which the antibodies were raised is bound. Those of skill in the art will know of various techniques common in the immunology arts for purification and/or concentration of polyclonal antibodies, as well as monoclonal antibodies (See for example, Coligan et al., Unit 9, *Current Protocols in Immunology*, Wiley Interscience, 1991).

25   It is also possible to use the anti-idiotype technology to produce monoclonal antibodies which mimic an epitope. For example, an anti-idiotypic monoclonal antibody made to a first monoclonal antibody will have a binding domain in the hypervariable region that is the "image" of the epitope bound by the first monoclonal antibody.

30   Effector molecules, e.g., therapeutic, diagnostic, or detection moieties, can be linked to an antibody that specifically binds a JMHV polypeptide, using any number of means known to those of skill in the art. Both covalent and noncovalent attachment means may be used. The procedure for attaching an effector molecule to

an antibody varies according to the chemical structure of the effector. Polypeptides typically contain a variety of functional groups; e.g., carboxylic acid (COOH), free amine ($-NH_2$) or sulfhydryl (-SH) groups, which are available for reaction with a suitable functional group on an antibody to result in the binding of the effector

5   molecule. Alternatively, the antibody is derivatized to expose or attach additional reactive functional groups. The derivatization may involve attachment of any of a number of linker molecules such as those available from Pierce Chemical Company, Rockford, IL. The linker can be any molecule used to join the antibody to the effector molecule. The linker is capable of forming covalent bonds to both the

10   antibody and to the effector molecule. Suitable linkers are well known to those of skill in the art and include, but are not limited to, straight or branched-chain carbon linkers, heterocyclic carbon linkers, or peptide linkers. Where the antibody and the effector molecule are polypeptides, the linkers may be joined to the constituent amino acids through their side groups (such as through a disulfide linkage to

15   cysteine) or to the alpha carbon amino and carboxyl groups of the terminal amino acids.

In some circumstances, it is desirable to free the effector molecule from the antibody when the immunoconjugate has reached its target site. Therefore, in these circumstances, immunoconjugates will comprise linkages that are cleavable in the

20   vicinity of the target site. Cleavage of the linker to release the effector molecule from the antibody may be prompted by enzymatic activity or conditions to which the immunoconjugate is subjected either inside the target cell or in the vicinity of the target site.

In view of the large number of methods that have been reported for attaching

25   a variety of radiodiagnostic compounds, radiotherapeutic compounds, label (e.g. enzymes or fluorescent molecules) drugs, toxins, and other agents to antibodies, one skilled in the art will be able to determine a suitable method for attaching a given effector molecule to an antibody or other polypeptide.

The immunoconjugates can be prepared by cloning techniques. Examples of

30   appropriate cloning and sequencing techniques, and instructions sufficient to direct persons of skill through many cloning exercises are found in Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2nd Ed.), Vols. 1-3, Cold Spring Harbor Laboratory (1989), Berger and Kimmel (eds.), *Guide to Molecular Cloning*

Techniques, Academic Press, Inc., San Diego CA (1987), or Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, Greene Publishing and Wiley-Interscience, NY (1987). Product information from manufacturers of biological reagents and experimental equipment also provide useful information. Such manufacturers

5   include the SIGMA chemical company (Saint Louis, MO), R&D systems (Minneapolis, MN), Pharmacia LKB Biotechnology (Piscataway, NJ), CLONTECH Laboratories, Inc. (Palo Alto, CA), Chem Genes Corp., Aldrich Chemical Company (Milwaukee, WI), Glen Research, Inc., GIBCO BRL Life Technologies, Inc. (Gaithersburg, MD), Fluka Chemica-Biochemika Analytika (Fluka Chemie AG,

10   Buchs, Switzerland), Invitrogen (San Diego, CA), and Applied Biosystems (Foster City, CA), as well as many other commercial sources known to one of skill.

Nucleic acids encoding native effector molecules or anti-JMHV antibodies can be modified to form the effector molecule, antibodies, or immunoconjugates. Modification by site-directed mutagenesis is well known in the art. Nucleic acids

15   encoding effector molecule or anti-JMHV antibodies can be amplified by *in vitro* methods. Amplification methods include the polymerase chain reaction (PCR), the ligase chain reaction (LCR), the transcription-based amplification system (TAS), the self-sustained sequence replication system (3SR). A wide variety of cloning methods, host cells, and *in vitro* amplification methodologies are well known in the

20   art.

In one embodiment, immunoconjugates are prepared by inserting a cDNA which encodes an anti-JMHV polypeptide scFv antibody into a vector which comprises the cDNA encoding the effector molecule. The insertion is made so that the scFv and the EM are read in frame that is in one continuous polypeptide which

25   contains a functional Fv region and a functional EM region

In addition to recombinant methods, the immunoconjugates, effector molecules, and antibodies can also be constructed in whole or in part using standard peptide synthesis. Solid phase synthesis of the polypeptides of less than about 50 amino acids in length may be accomplished by attaching the C-terminal amino acid

30   of the sequence to an insoluble support followed by sequential addition of the remaining amino acids in the sequence. Techniques for solid phase synthesis are described by Barany & Merrifield, "The Peptides: Analysis, Synthesis, Biology," Vol. 2, *Special Methods in Peptide Synthesis*, Part A. pp. 3-284; Merrifield et al. *J.*

Am. Chem. Soc. 85:2149-2156, 1963, and Stewart et al., *Solid Phase Peptide Synthesis*, 2nd ed., Pierce Chem. Co., Rockford, IL, 1984. Proteins of greater length may be synthesized by condensation of the amino and carboxyl termini of shorter fragments. Methods of forming peptide bonds by activation of a carboxyl terminal

5   end (e.g., by the use of the coupling reagent N, N'-dicycylohexylcarbodiimide) are known to those of skill.

Once the nucleic acids encoding an EM, anti-JMHV antibody, or an immunoconjugate, are isolated and cloned, one may express the desired protein in a recombinantly engineered cell such as bacteria, plant, yeast, insect and mammalian

10   cells. It is expected that those of skill in the art are knowledgeable in the numerous expression systems available for expression of proteins including *E. coli,* other bacterial hosts, yeast, and various higher eukaryotic cells such as the COS, CHO, HeLa and myeloma cell lines.

Antibodies can be covalently or non-covalently linked to a detectable label.

15   Detectable labels suitable for such use include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present disclosure include magnetic beads (e.g. DYNABEADS)̇, fluorescent dyes (e.g., fluorescein isothiocyanate, Texas red, rhodamine, green fluorescent protein, and the like), radiolabels (e.g., ^{3}H, ^{125}I, ^{35}S,

20   ^{14}C, or ^{32}P), enzymes (e.g., horseradish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads. Means of detecting such labels are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film or scintillation

25   counters, fluorescent markers may be detected using a photodetector to detect emitted illumination. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate, and colorimetric labels are detected by simply visualizing the colored label.

30

Diagnostic Methods

A method for screening a subject to determine if the subject has been infected with JMHV is disclosed herein. One major application of the JMHV sequence information presented herein is in the area of diagnostic testing for

5   predisposition to a disease (such as for multiple sclerosis) that develops in at least a subset of hosts infected with JMHV. The nucleic acid sequence of the JMHV ORFs is also useful in such diagnostic methods. The method includes providing a biological sample obtained from the subject, in which sample includes DNA or RNA, and providing an assay for detecting in the biological sample the presence of

10   any of the JMHV nucleic acids or proteins. Suitable biological samples include samples obtained from body cells, such as those present in peripheral blood, urine, saliva, tissue biopsy, surgical specimen, fine needle aspirate specimen, amniocentesis samples and autopsy material. The detection in the biological sample may be performed by a number of methodologies, as outlined below.

15   The foregoing assay may be assembled in the form of a diagnostic kit and preferably comprises either: hybridization with oligonucleotides; PCR amplification of the gene or a part thereof using oligonucleotide primers; RT-PCR amplification of the RNA or a part thereof using oligonucleotide primers; or direct sequencing of any of the JMHV genes present in a subject using oligonucleotide primers. The

20   efficiency of these molecular genetic methods should permit the rapid identification of patients infected with JMHV. Thus kits can include containers with JMHV nucleic acid sequences (such as probes or primers) and/or containers including an antibody that specifically binds JMHV.

One embodiment of such detection techniques is the polymerase chain

25   reaction amplification of reverse transcribed RNA (RT-PCR) of RNA isolated from cells (for example lymphocytes) followed by direct DNA sequence determination of the products. The presence of one or more JMHV genes is taken an indicative of potential JMHV infection.

Alternatively, DNA extracted from lymphocytes or other cells may be used

30   directly for amplification. The direct amplification from genomic DNA would be appropriate for analysis of an entire JMHV nucleic acid sequence including regulatory sequences located upstream and downstream from the open reading

frame. Recent reviews of direct DNA diagnosis have been presented by Caskey (*Science* 236:1223-1228, 1989) and by Landegren et al. (*Science* 242:229-37, 1989). DNA diagnostic methods to specifically detect an ORF, or to detect a particular polymorphism in an ORF, can be designed.

5   The detection of specific DNA mutations or alterations in gene sequences may be achieved by methods such as hybridization using specific oligonucleotides (Wallace et al., *Cold Spring Harbor Symp. Quant. Biol.* 51:257-61, 1986), direct DNA sequencing (Church and Gilbert, *Proc. Natl. Acad. Sci. USA.* 81:1991-5, 1984), the use of restriction enzymes (Flavell et al., *Cell* 15:25, 1978; Geever et al.,

10   *Proc. Natl. Acad. Sci USA* 78:5081, 1981), discrimination on the basis of electrophoretic mobility in gels with denaturing reagent (Myers and Maniatis, *Cold Spring Harbor Symp. Quant. Biol.* 51:275-284, 1986), RNase protection (Myers et al., *Science* 230:1242, 1985), chemical cleavage (Cotton et al., *Proc. Natl. Acad. Sci. USA* 85:4397-401, 1985), and the ligase-mediated detection procedure (Landegren et

15   al., *Science* 241:1077, 1988).

Oligonucleotides specific to normal, mutant or alterative sequences are chemically synthesized using commercially available machines, labeled radioactively with isotopes (such as ^{32}P) or non-radioactively, with tags such as biotin (Ward and Langer et al., *Proc. Natl. Acad. Sci. USA* 78:6633-57, 1981), and

20   hybridized to individual DNA samples immobilized on membranes or other solid supports by dot-blot or transfer from gels after electrophoresis. The presence of these specific sequences are visualized by methods such as autoradiography or fluorometric (Landegren et al., *Science* 242:229-37, 1989) or colorimetric reactions (Gebeyehu et al., *Nucleic Acids Res.* 15:4513-34, 1987). The absence of

25   hybridization would indicate a mutation in the particular region of the gene, or that the patient is not infected with JMHV.

Sequence differences between disclosed and other forms of JMHV genes may also be revealed by the direct DNA sequencing method of Church and Gilbert (*Proc. Natl. Acad. Sci. USA* 81:1991-5, 1988). Cloned DNA segments may be used

30   as probes to detect specific DNA segments. The sensitivity of this method is greatly enhanced when combined with PCR (Wrichnik et al., *Nucleic Acids Res.* 15:529-42, 1987; Wong et al., *Nature* 330:384-6, 1987; Stoflet et al., *Science* 239:491-4, 1988). In this approach, a sequencing primer which lies within the amplified sequence is

used with double-stranded PCR product or single-stranded template generated by a modified PCR. The sequence determination is performed by conventional procedures with radiolabelled nucleotides or by automatic sequencing procedures with fluorescent tags.

5   . Sequence alterations may occasionally generate fortuitous restriction enzyme recognition sites or may eliminate existing restriction sites. Changes in restriction sites are revealed by the use of appropriate enzyme digestion followed by conventional gel-blot hybridization (Southern, *J. Mol. Biol.* 98:503, 1975). DNA fragments carrying the site (either normal, mutant, or alternative) are detected by

10   their reduction in size or increase of corresponding restriction fragment numbers. Genomic DNA samples may also be amplified by PCR prior to treatment with the appropriate restriction enzyme; fragments of different sizes are then visualized under UV light in the presence of ethidium bromide after gel electrophoresis.

           Screening based on DNA sequence differences may be achieved by detection

15   of alteration in electrophoretic mobility of DNA fragments in gels with or without denaturing reagent. Small sequence deletions and insertions can be visualized by high-resolution gel electrophoresis. For example, a PCR product with small deletions is clearly distinguishable from a normal sequence on an 8% non-denaturing polyacrylamide gel (WO 91/10734; Nagamine et al., *Am. J. Hum. Genet.*

20   45:337-9, 1989). DNA fragments of different sequence compositions may be distinguished on denaturing formamide gradient gels in which the mobilities of different DNA fragments are retarded in the gel at different positions according to their specific "partial-melting" temperatures (Myers et al., *Science* 230:1242, 1985). Alternatively, a method of detecting a mutation comprising a single base substitution

25   or other small change could be based on differential primer length in a PCR. For example, an invariant primer could be used in addition to a primer specific for a mutation. The PCR products of the normal and mutant genes can then be differentially detected in acrylamide gels.

           In addition to conventional gel-electrophoresis and blot-hybridization

30   methods, DNA fragments may also be visualized by methods where the individual DNA samples are not immobilized on membranes. The probe and target sequences may be both in solution, or the probe sequence may be immobilized (Saiki et al., *Proc. Nat. Acad. Sci. USA* 86:6230-4, 1989). A variety of detection methods, such

as autoradiography involving radioisotopes, direct detection of radioactive decay (in the presence or absence of scintillant), spectrophotometry involving calorigenic reactions and fluorometry involved fluorogenic reactions, may be used to identify specific individual genotypes.

5   If more than one mutation or alternative sequence is frequently encountered in one or more JMHV genes, a system capable of detecting such multiple mutations can be produced. For example, a PCR with multiple, specific oligonucleotide primers and hybridization probes can be used to identify all possible mutations or alternative sequences at the same time (Chamberlain et al., *Nucl. Acids Res.*

10   16:1141-55, 1988). The procedure may involve immobilized sequence-specific oligonucleotides probes (Saiki et al., *Proc. Nat. Acad. Sci. USA* 86:6230-4, 1989).

Quantitation of JMHV Proteins

An alternative method of determining if a subject has been infected with

15   RRV or JMHV is to quantitate the level of one or more RRV (or JMHV) proteins in the cells of a subject. This diagnostic tool would also be useful for detecting the levels of the JMHV proteins which result from infection by JMHV. These diagnostic methods provide an enhanced ability to diagnose susceptibility to diseases caused by JMHV infection.

20   The determination of JMHV protein levels would be an alternative or supplemental approach to the direct determination of the presence of one or more JMHV genes. The availability of antibodies specific to one or more of the JMHV proteins will facilitate the quantitation of cellular JMHV proteins by one of a number of immunoassay methods which are well known in the art and are presented

25   in Harlow and Lane (*Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, New York., 1988).

Such assays permit the detection of JMHV proteins in a biological sample and the quantitation of such proteins. Typical methods involve: providing a biological sample of the subject in which the sample contains cellular proteins, and

30   providing an immunoassay for quantitating the level of at least one JMHV protein in the biological sample. This can be achieved by combining the biological sample with a JMHV specific binding agent, such as an antibody (e.g. monoclonal or

polyclonal antibodies that bind a JMHV protein), so that complexes form between the binding agent and the viral protein present in the sample, and then detecting or quantitating such complexes.

In particular forms, these assays may be performed with the JMHV specific

5   binding agent immobilized on a support surface, such as in the wells of a microtiter plate or on a column. The biological sample is then introduced onto the support surface and allowed to interact with the specific binding agent so as to form complexes. Excess biological sample is then removed by washing, and the complexes are detected with a reagent, such as a second anti-JMHV protein

10   antibody, that is conjugated with a detectable marker.

In an alternative assay, the cellular proteins are isolated and subjected to SDS-PAGE followed by Western blotting. After resolving the proteins, the proteins are transferred to a membrane, which is probed with specific binding agents that recognize any of the JMHV proteins. The proteins are detected, for example with

15   labeled (such as horseradish peroxidase, HRP)-conjugated secondary antibodies, and quantitated.

In yet another assay, the level of one or more JMHV proteins in cells is analyzed using microscopy. Using specific binding agents which recognize JMHV, samples can be analyzed for the presence of one or more JMHV proteins. For

20   example, frozen biopsied tissue sections are thawed at room temperature and fixed with acetone at -200°C for 5 minutes. Slides are washed twice in cold PBS for 5 minutes each, then air-dried. Sections are covered with 20-30 µl of antibody solution (15-45 µg/ml) (diluted in PBS, 2% BSA at 15-50 µg/ml) and incubated at room temperature in humidified chamber for 30 minutes. Slides are washed three

25   times with cold PBS 5 minutes each, allowed to air-dry briefly (5 minutes) before applying 20-30 µl of the second antibody solution (diluted in PBS, 2% BSA at 15-50 µg/ml) and incubated at room temperature in humidified chamber for 30 minutes. The label on the second antibody may contain a fluorescent probe, enzyme, radiolabel, biotin, or other detectable marker. The slides are washed three times

30   with cold PBS 5 minutes each then quickly dipped in distilled water, air-dried, and mounted with PBS containing 30% glycerol. Slides can be stored at 4°C prior to viewing.

For samples prepared for electron microscopy (versus light microscopy), the second antibody is conjugated to gold particles. Tissue is fixed and embedded with epoxy plastics, then cut into very thin sections (~1-2 μm). The specimen is then applied to a metal grid, which is then incubated in the primary anti-JMHV antibody,

5   washed in a buffer containing BSA, then incubated in a secondary antibody conjugated to gold particles (usually 5-20 nm). These gold particles are visualized using electron microscopy methods.

For the purposes of quantitating the JMHV proteins, a biological sample of the subject, which sample includes cellular proteins, is required. Such a biological

10   sample may be obtained from body cells, such as those present in which expression of the protein has been detected. The expression of JMHV proteins in peripheral blood leukocytes is clearly the most accessible and convenient source from which specimens can be obtained. Specimens can be obtained from peripheral blood, urine, saliva, tissue biopsy, amniocentesis samples, surgical specimens, fine needle

15   aspirates, and autopsy material, particularly cancer cells. Quantitation of JMHV proteins would be made by immunoassay and compared to levels of the protein found in non-JMHV expressing cells, or to the level of JMHV proteins in non-JMHV infected cells (cells of the same origin that are not infected). A significant (preferably 50% or greater) increase in the amount of one or more JMHV proteins in

20   the cells of a subject compared to the amount of one or more JMHV proteins found in non-JMHV infected cells or that found in normal cells, would be taken as an indication that the subject may have been infected with JMHV.

Screening Assays for Pharmaceutical Agents of Interest

25   The present disclosure provides a virus that is involved in the causation or progression of certain diseases, such as multiple sclerosis, and therefore provides an animal model and assays directed to identifying potential pharmaceutical agents that inhibit the biological activity of the virus. Drug screening assays which determine whether or not a drug has activity against the virus can include incubating a

30   compound to be evaluated for use in treatment of the condition with cells which express the JMHV proteins or peptides, and determining the effect of the compound on the activity of the virus. *In vitro* assays in which the virus is maintained in

suitable cell culture are provided as are *in vivo* animal models (such as a non-human primate model).

In vitro assays include infecting cells such as Japanese macaque fibroblasts, neuronal cells, peripheral blood leukocytes or susceptible B or T cell lines with the

5   agent of interest in the presence of varying concentrations of compounds targeted against viral replication. These compounds include, but are not limited to nucleoside analogs, chain terminators, antisense oligonucleotides and random polypeptides. (Asada et al., *J. Clin. Microbiol.* 27:2204, 1989; Kikuta et al., *Lancet* 7:861, 1989). Infected cultures and their supernatants can be assayed for the total

10   amount of virus, including the presence of the viral genome, by quantitative PCR, by dot blot assays, or by using immunologic methods. For example, a culture of susceptible cells could be infected with the JMHV in the presence of various concentrations of drug, fixed on slides after a period of days, and examined for viral antigen by indirect immunofluorescence with monoclonal antibodies to viral

15   polypeptides. Alternatively, chemically adhered cell monolayers can be used for an infectious agent assay using indirect immunofluorescent antibody staining to search for focus reduction (Higashi, *J. Clin. Microbiol.* 27:2204, 1989, incorporated by reference).

As an alternative to whole cell *in vitro* assays, purified enzymes isolated

20   from the JMHV can be used as targets for rational drug design to determine the effect of the potential drug on enzyme activity, such as thymidylate sunthase or DNA polymerase. A measure of enzyme activity indicates an effect on the infectious agent itself. Drug screens using herpes viral products are known and have been previously described in EP 0514830 (herpes proteases) and WO 94/04920 (U_L

25   13 gene product).

In particular embodiments, this disclosure provides an assay for screening anti-MS chemotherapeutics. Infected cells can be incubated in the presence of a chemical agent that is a potential chemotherapeutic against MS. The level of virus in the cells is then determined after several days by IFA for antigens or Southern

30   blotting for viral genome or Northern blotting for mRNA and compared to control cells. This assay can quickly screen large numbers of chemical compounds that may be useful against MS. This disclosure also provides an assay system that is employed to identify drugs or other molecules capable of binding to the DNA

molecule or proteins, either in the cytoplasm or in the nucleus, thereby inhibiting or potentiating transcriptional activity. This assay would be useful in the development of drugs that are specific against particular cellular activity, or that would potentiate such activity, in time or in level of activity. Also included are drugs identified by

5   this assay which have an anti-viral activity, and have therapeutic value for conditions associated with JMHV infection.

Thus, an assay is provided herein for screening anti-multiple sclerosis (MS) therapeutics. Infected cells can be incubated in the presence of a chemical agent that is a potential anti-inflammatory agent or other agent of use in treating MS (such as

10   an agent that alters the interaction of IL-2 with its receptor). The level of virus in the cells is then determined by IFA for antigens, Southern blotting for the viral genome, Northern blotting for mRNA, or PCR, and compared to control cell. This assay can quickly screen large numbers of agents that may be useful in the treatment of MS. This disclosure also provides an assay system that is employed to identify

15   drugs or other molecules capable of binding to the DNA molecule or proteins, either in the cytoplasm or in the nucleus, thereby inhibiting or potentiating transcriptional activity. This assay would be useful in the development of drugs that are specific against particular cellular activity, or that would potentiate such activity, in time or in level of activity. Also included are drugs identified by this assay which have an

20   anti-viral activity, and an effect against conditions associated with JMHV infection, such as MS.

Animal models are useful for resolving a number of fundamental problems of infectious diseases that include, but are not limited to, determinants of virulence of the organism, mechanisms of host resistance, mechanisms of pathogenicity,

25   establishment and regulation of chronic infection, and antimicrobial and chemotherapeutic actions of drugs on infectious agents. Variables that are commonly manipulated to address fundamental problems include, but are not limited to, the strain of infectious agent, the infecting dose of infectious agent and the route of administration of the infectious agent, the species or subspecies of animal, the age

30   of animal, and the genetic background of the animal (Viral pathogenesis, N. Nathanson, Lippincot-Raven, Philadelphia, PA, 1997).

Multiple sclerosis (MS) is a chronic, debilitating inflammatory disease limited to central nervous system (CNS) white matter. Currently, there are very few

effective treatments for MS. The disease may not be etiologically homogeneous, but rather a complex set of diseases that have in common pathogenic mechanisms that involve genetically predisposed individuals, and infectious agents as initiators and diverse mechanisms of inflammatory white matter destruction (Hafler, *J Clin Invest*

5   104:527-529, 1999). Genetic studies in families with MS-affected members have revealed that MS is a complex trait, that the contribution of individual genes to susceptibility is probably small, and that differences are possible between familial and sporadic forms of the disease (Kalman and Lublin, *Biomed Pharmacother* 53:358-370, 1999).

10   An animal model, including a Japanese macaque infected with a virus at least 90% identical to the nucleic acid sequence set forth as SEQ ID NO: 1 is provided herein. This animal model can be used to assess the efficacy of agents for the treatment of multiple sclerosis.

           In another embodiment, in which one or more JMHV strains are employed

15   for generating an animal model, the JMHV used may be naturally occurring variant isolates recovered from Japanese macaques and other non-human primate species, molecular clones generated from these naturally occurring variant isolates and recombinant viruses with introduced mutations, deletions or recombined genomes designed to address function of specific genes.   For example, the JMHV can include

20   a nucleic acid sequence set forth as SEQ ID NO: 1. To create the animal model, an animal, such as a non-human primate, is utilized. For example, a macaque monkey can be administered JMVH. The non-human animal is administered a JMVH by any route, including oral, inhalation, intratracheal, intravaginal, intrarectal and parenteral routes including, but not limited to intravenous, intraarterial, intradermal,

25   subcutaneous, intramuscular, intraperitoneal and organ-specific administration routes such and intracerebral and intraocular administration. The effect of an agent can then be evaluated in the animal. The agent can be administered prior to infection with the virus, at the same time as infection with the virus, or after infection with the virus. A therapeutically effective amount of the agent is

30   administered, and a signs, symptom, or parameter of viral infection (such as viral load or expression of a JMHV protein) is assessed. In one embodiment, the sign, symptom, or a parameter of viral infection is compared to a control, such as to an

animal of the same species infected with JMHV that is not treated with the agent, is treated with a vehicle control, or is not infected with JMHV.

Pharmaceutical Compositions and Use

Pharmaceutical compositions including JMHV nucleic acid sequences, JMHV proteins, or antibodies that bind these proteins are disclosed herein.

These pharmaceutical compositions include a therapeutically effective amount of one or more JMHV polypeptide, or a nucleic acid encoding a JMHV polypeptide, or an antibody that specifically binds a JMHV polypeptide, alone or in combination, in conjunction with a pharmaceutically acceptable carrier.

Disclosed herein are substances suitable for use as vaccines for the prevention of diseases associated with JMHV infection, such as MS, and methods for administering them. Particular vaccines are directed against JMHV or related viruses, and may include antigens obtained from JMHV or its related viruses. In one embodiment, the vaccine contains attenuated JMHV, or related viruses found in humans. In another embodiment, the vaccine contains killed JMHV. In another embodiment, the vaccine contains a nucleic acid vector encoding at least one JMHV ORF, such as a surface protein of JMHV. In another embodiment, the composition contains a JMHV subunit, such as glycoprotein B, major capsid protein, or other gene products found to elicit appropriate humoral and/or cell mediated immune responses.

Various delivery systems for administering pharmaceutical compositions including JMHV proteins include encapsulation in liposomes, microparticles, microcapsules, expression by recombinant cells, receptor-mediated endocytosis (see Wu and Wu, *J. Biol. Chem.* 262:4429-32, 1987), and construction of a therapeutic nucleic acid (such as an anti-sense molecule) as part of a retroviral or other vector. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, the pharmaceutical compositions may be introduced into the central

nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

5   The use of liposomes as a delivery vehicle is another delivery method of the present disclosure. The liposomes fuse with the target site and deliver the contents of the lumen intracellularly. The liposomes are maintained in contact with the target cells for a sufficient time for fusion to occur, using various means to maintain contact, such as isolation and binding agents. Liposomes may be prepared with purified proteins or peptides that mediate fusion of membranes, such as Sendai virus

10   or influenza virus. The lipids may be any useful combination of known liposome forming lipids, including cationic lipids, such as phosphatidylcholine. Other potential lipids include neutral lipids, such as cholesterol, phosphatidyl serine, phosphatidyl glycerol, and the like. For preparing the liposomes, the procedure described by Kato et al. (*J. Biol. Chem.* 266:3361, 1991) may be used.

15   The pharmaceutical compositions or methods of treatment may be administered in combination with other therapeutic treatments, such as with additional immunosuppressive therapies.

JMHV nucleic acids can be used to generate an animal model, or to express JMHV polypeptides to produce an immune response against JMHV. In an

20   embodiment in which one or more JMHV nucleic acids are employed for generating an animal model, or for producing an immune response, the nucleic acid can be delivered intracellularly (e.g., by expression from a nucleic acid vector or by receptor-mediated mechanisms). In a specific embodiment where the therapeutic molecule is a nucleic acid, administration may be achieved by an appropriate nucleic

25   acid expression vector which is administered so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the

30   nucleus (see e.g., Joliot et al., *Proc. Natl. Acad. Sci. USA* 88:1864-8, 1991). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The vector pCDNA, is an example of a method of introducing the foreign cDNA into a cell under the control of a strong viral promoter (CMV) to drive the expression. However, other vectors can be used. Other retroviral vectors (such as pRETRO-ON, Clontech), also use this promoter but have the advantages of entering

5   cells without any transfection aid, integrating into the genome of target cells only when the target cell is dividing (as cancer cells do, especially during first remissions after chemotherapy) and they are regulated. It is also possible to turn on the expression of the RRV or JMHV nucleic acid by administering tetracycline when these plasmids are used. Hence these plasmids can be allowed to transfect the cells,

10   then administer a course of tetracycline with a course of chemotherapy to achieve better cytotoxicity.

Other plasmid vectors, such as pMAM-neo (also from Clontech) or pMSG (Pharmacia) use the MMTV-LTR promoter (which can be regulated with steroids) or the SV10 late promoter (pSVL, Pharmacia) or metallothionein-responsive

15   promoter (pBPV, Pharmacia) and other viral vectors, including retroviruses. Examples of other viral vectors include adenovirus, AAV (adeno-associated virus), recombinant HSV, poxviruses (vaccinia) and recombinant lentivirus (such as HIV). All these vectors achieve the basic goal of delivering into the target cell the cDNA sequence and control elements needed for transcription. The present disclosure

20   includes all forms of nucleic acid delivery, including synthetic oligos, naked DNA, plasmid and viral, integrated into the genome or not.

Also contemplated are inhibitory nucleic acid therapeutics that can inhibit the activity of JMHV, for example in a subject with MS or other diseases associated with JMHV infection. Inhibitory nucleic acids may be single-stranded nucleic acids,

25   which can specifically bind to a complementary nucleic acid sequence. By binding to the appropriate target sequence, an RNA-RNA, a DNA-DNA, or RNA-DNA duplex or triplex is formed. These nucleic acids are often termed "antisense" because they are usually complementary to the sense or coding strand of the gene, although recently approaches for use of "sense" nucleic acids have also been

30   developed. The term "inhibitory nucleic acids" as used herein, refers to both "sense" and "antisense" nucleic acids, and includes small inhibitory RNAs.

By binding to the target nucleic acid, the inhibitory nucleic acid can inhibit the function of the target nucleic acid. This could, for example, be a result of

blocking DNA transcription, processing or poly(A) addition to mRNA, DNA replication, translation, or promoting inhibitory mechanisms of the cells, such as promoting RNA degradation. Inhibitory nucleic acid methods therefore encompass a number of different approaches to altering expression of JMHV genes. Cleavage,

5   and therefore inactivation, of the target nucleic acids may be effected by attaching a substituent to the inhibitory nucleic acid which can be activated to induce cleavage reactions. The substituent can be one that affects either chemical, or enzymatic cleavage. Alternatively, cleavage can be induced by the use of ribozymes or catalytic RNA. In this approach, the inhibitory nucleic acids would include either

10   naturally occurring RNA (ribozymes) or synthetic nucleic acids with catalytic activity.

       The inhibitory nucleic acid therapies can be used to target nucleic acids to sequences of JMHV for use in treating conditions caused by the JMHV, or proteins of the JMHV, for example for treating MS or an other immune mediated syndromes,

15   such as an autoimmune disease.

       Therapeutic, intravenous, polyclonal or monoclonal antibodies have been used as a mode of passive immunotherapy of herpesviral diseases, such as infection with CMV. Immune globulin from subjects previously infected with the JMHV and bearing a suitably high titer of antibodies against the virus can be given in

20   combination with antiviral agents (e.g. ganciclovir), or in combination with other modes of immunotherapy that are currently being evaluated for the treatment of MS, which are targeted to modulating the immune response (such as treatment with antibodies that inhibit the interaction of IL-2 with its receptor). In one embodiment, antibodies specific for an epitope expressed on cells infected with the JMHV are

25   utilized and can be obtained as described above.

       Thus, pharmaceutical compositions which include a therapeutically effective amount of an antibody, and a pharmaceutically acceptable carrier or excipient. The antibody can be polyclonal or monoclonal.

30   A method is provided herein for vaccinating a subject against multiple sclerosis, comprising administering to a susceptible subject an effective amount of the peptide or polypeptide encoded by an isolated DNA molecule encoding a polypeptide or combination of polypeptides expressed by the DNA molecule, and a

suitable acceptable carrier. In one embodiment, DNA is administered to the subject in an effective amount to vaccinate the subject against multiple sclerosis, or other disease associated with JMHV infection.

5   The vaccine can be made using synthetic peptide or recombinantly-produced polypeptide described above as antigen. Typically, a vaccine will include from about 1 to 50 micrograms of antigen, for example from about 15 to about 45 micrograms. Typically, the vaccine is formulated so that a dose includes about 0.5 milliliters. The vaccine may be administered by any route known in the art, for example parenteral, subcutaneous or intramuscular.

10   There are a number of strategies for amplifying an antigen's effectiveness, particularly as related to the art of vaccines. For example, cyclization of a peptide can increase the peptide's antigenic and immunogenic potency. See U.S. Patent No. 5,001,049. More conventionally, an antigen can be conjugated to a suitable carrier, usually a protein molecule. This procedure can allow multiple copies of an antigen, 15   such as a peptide, to be conjugated to a single larger carrier molecule. Additionally, the carrier may possess properties which facilitate transport, binding, absorption or transfer of the antigen.

For parenteral administration, such as subcutaneous injection, examples of suitable carriers are the tetanus toxoid, the diphtheria toxoid, serum albumin and 20   lamprey, or keyhole limpet, hemocyanin because they provide the resultant conjugate with minimum genetic restriction. Conjugates including these universal carriers can function as T cell clone activators in individuals having very different gene sets. The conjugation between a peptide and a carrier can be accomplished using one of the methods known in the art. Specifically, the conjugation can use 25   bifunctional cross-linkers as binding agents as detailed, for example, by Means and Feeney, "A recent review of protein modification techniques," *Bioconjugate Chem.* 1:2-12, 1990.

Vaccines against JMHV can be made from the JMHV envelope glycoproteins. These proteins can be purified and used for vaccination (Lasky, *J.* 30   *Med. Virol.* 31:59, 1990). MHC-binding peptides from cells infected with the human herpesvirus can be identified for vaccine candidates per the methodology of Marloes et al., *Eur. J. Immunol.*21:2963-2970, 1991. The JMHV antigen may be combined or mixed with various solutions and other compounds as is known in the

art. For example, it may be administered in water, saline or buffered vehicles with or without various adjuvants or immunodiluting agents. Examples of such adjuvants or agents include aluminum hydroxide, aluminum phosphate, aluminum potassium sulfate (alum), beryllium sulfate, silica, kaolin, carbon, water-in-oil emulsions, oil-

5   in-water emulsions, muramyl dipeptide, bacterial endotoxin, lipid X, Corynebacterium parvum (Propionibacterium acnes), Bordetella pertussis, polyribonucleotides, sodium alginate, lanolin, lysolecithin, vitamin A, saponin, liposomes, levamisole, DEAE-dextran, blocked copolymers or other synthetic adjuvants. Such adjuvants are available commercially from various sources, for

10   example, Merck Adjuvant 65 (Merck and Company, Inc., Rahway, N.J.) or Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI). Other suitable adjuvants are Amphigen (oil-in-water), Alhydrogel (aluminum hydroxide), or a mixture of Amphigen and Alhydrogel. Only aluminum is approved for human use.

15   The proportion of antigen and adjuvant can be varied over a broad range so long as both are present in effective amounts. For example, aluminum hydroxide can be present in an amount of about 0.5% of the vaccine mixture (Al_2O_3 basis). On a per-dose basis, the amount of the antigen can range from about 0.1 μg to about 100 μg protein per subject, for example about 1 μg to about 50 μg per dose, or about 15

20   μg to about 45 μg. A suitable dose size is about 0.5 ml. Accordingly, a dose for intramuscular injection, for example, would comprise 0.5 ml containing 45 μg of antigen in admixture with 0.5% aluminum hydroxide. After formulation, the vaccine may be incorporated into a sterile container which is then sealed and stored at a low temperature, for example 4°C., or it may be freeze-dried. Lyophilization

25   permits long-term storage in a stabilized form.

The vaccines may be administered by any conventional method for the administration of vaccines including oral and parenteral (e.g., subcutaneous or intramuscular) injection. Intramuscular administration is preferred. The treatment may consist of a single dose of vaccine or a plurality of doses over a period of time.

30   Also, the antigen could be a component of a recombinant vaccine which is adaptable for oral administration. Vaccines of the disclosure may be combined with other vaccines for other diseases to produce multivalent vaccines. A pharmaceutically

effective amount of the antigen can be employed with a pharmaceutically acceptable carrier such as a protein or diluent useful for the vaccination of mammals, particularly humans. Other vaccines may be prepared according to methods well-known to those skilled in the art.

5   Those of skill will readily recognize that it is only necessary to expose a mammal to appropriate epitopes in order to elicit effective immunoprotection. The epitopes are typically segments of amino acids which are a small portion of the whole protein. Using recombinant genetics, it is routine to alter a natural protein's primary structure to create derivatives embracing epitopes that are identical to or

10   substantially the same as (immunologically equivalent to) the naturally occurring epitopes. Such derivatives may include peptide fragments, amino acid substitutions, amino acid deletions and amino acid additions of the amino acid sequence for the viral polypeptides from the human herpesvirus. For example, it is known in the protein art that certain amino acid residues can be substituted with amino acids of

15   similar size and polarity without an undue effect upon the biological activity of the protein. The human herpesvirus proteins have significant tertiary structure and the epitopes are usually conformational. Thus, modifications should generally preserve conformation to produce a protective immune response.

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           The disclosure is illustrated by the following non-limiting Examples.

EXAMPLES

Japanese macaque herpesvirus (JMHV) was isolated from a monkey with encephalomyelitis and the complete nucleotide sequence was determined. DNA
5   sequence and phylogenetic analysis revealed JMHV is a gamma-2 herpesvirus. JMHV was associated with demyelinating disease *in vivo*. The virus can also be propagated *in vitro*. As disclosed herein the entire genome of a novel gamma herpesvirus, referred to as Japanese macaque herpesvirus (JMHV) has been identified and sequenced. The virus was isolated from an inflamed spinal cord
10   lesion obtained from a Japanese macaque with spontaneous MS-like disease.

Rhesus macaques naturally harbor a virus related to KSHV, referred to as RRV, for rhesus rhadinovirus. JMHV is related to RRV, which is described in International Application No. PCT/US99/26260 filed November 5, 1999, which claims priority from U.S. Provisional Application No. 60/109,409 filed November 20, 1998 and
15   U.S. Provisional Application No. 60/107,507 filed November 6, 1998, are also incorporated herein by reference

Example 1
20   ### Virus Isolation

Japanese macaque encephalomyelitis (JME) is a spontaneous demyelinating disease with clinical features such as ataxia and paralysis similar to those of MS. To investigate whether a virus is associated with the development of JME, a spinal cord lesion was obtained at necropsy from a macaque with JME, dissociated and cultured
25   with primary macaque fibroblasts. Cytopathic effects (CPE) developed in the culture after 10 days and the culture was harvested for passage. Primary macaque fibroblasts were inoculated with filtered extracts from the original culture and observed for CPE. Cultures developing CPE were harvested and analyzed by transmission electron microscopy (TEM) for the presence of virus particles. TEM
30   examination revealed 150-200 nm virus particles with characteristic dense cores resembling herpesviruses. Limiting dilution of the original virus isolate yielded a purified herpesvirus preparation, which was subsequently expanded for viral DNA

isolated and identified by degenerate PCR (Wucherpfennig and Strominger, *Cell* 80:695-705, 1995).

Example 2

5   **Sequence Analysis and Identification of Open Reading Frames**

Sequence analysis of the degenerate PCR product targeting the DNA polymerase gene revealed that the JMHV was closely related to rhesus macaque rhadinovirus (RRV) (Searles et al., *J Virol* 73:3040-53, 1999). To further identify the herpesvirus, a shotgun subclone library of the JMHV genome was generated and

10   the genomic sequence deduced as recently described for rhesus cytomegalovirus (Hansen et al, *J Virol* 77:6620-36, 2003). The complete JMHV sequence was compiled and analyzed using MacVector version 7.2 (Acelrys, San Diego, CA). The target search criterion was for open reading frames (ORFs) that encoded proteins of 80 amino acids or more. Putative ORFs were translated and homologous proteins

15   were identified using GenBank's BLASTP search engine. The full length nucleic acid sequence is shown in SEQ ID NO: 1.

Analysis of the JMHV DNA sequence indicated the genome is similar to all herpesviruses, has a linear, double-stranded DNA genome that is 131,217 base pairs in length and encodes 171 potential ORFs (Table 1, see also FIG. 1). The ORF

20   finder of MacVector was used to identify all 171 putative ORFs greater than or equal to 80 amino acids. Putative ORFs were numbered by the order in which they appear in the genome. In Table 1, ORFs that read left to right are designated W, whereas ORFs that read right to left are designated by C. ORFs from RRV strain 17577 (GenBank Accession No. AF083501) were used for comparison. The

25   complete JMHV genome sequence has been deposited in GenBank.

Table 1

JMHV ORF Summary

30

ORF	Strand	Position (nt)		Length		RRV	Description
		Fr m	To	b.p.	a.a	Hom log	
JM1	C	594	890	296	99		
JM2	W	1444	2721	1277	426	R1	IgG receptor
JM3	C	2778	3359	581	194	ORF 2	Dihydrofolate reductase
JM4	W	3526	4713	1187	396	ORF 4	Complement binding

ORF	Strand	From	To	b.p.	a.a	RRV Homolog	Description
							protein
JM5	W	5146	8544	3398	1133	ORF 6	ssDNA binding protein
JM6	C	5581	5895	314	105		
JM7	C	7410	7676	266	89		
JM8	C	7462	7722	260	87		
JM9	C	8541	8792	251	84		
JM10	W	8569	10629	2060	687	ORF 7	Processing/transport protein
JM11	C	10606	10929	323	108		
JM12	W	10616	13102	2486	829	ORF 8	Glycoprotein B
JM13	C	12565	12858	293	98		
JM14	W	13219	16257	3038	1013	ORF 9	DNA polymerase
JM15	C	13267	13827	560	187		
JM16	C	14809	15117	308	103		
JM17	W	15726	16031	305	102		
JM18	W	16351	17601	1250	417	ORF 10	
JM19	C	17226	17501	275	92		
JM20	W	17610	18839	1229	410	ORF 11	
JM21	C	19018	19641	623	208	R2	vIL-6
JM22	C	19861	20862	1001	334	ORF 70	Thymidylate synthetase
JM23	C	20969	21235	266	89		
JM24	C	21386	21748	362	121	R3	VMIP
JM25	C	21845	22120	275	92		HHV2 RS1; collagen-like, myosin XV
JM26	C	22363	22701	338	113		Myosin IA, sphingosine kinase
JM27	W	22700	23008	308	103		Similar to RRV ORF RU1-R
JM28	W	25392	25955	563	188	ORF 16	Bcl-2 homolog
JM29	C	26062	27672	1610	537	ORF 17	Capsid protein
JM30	W	27545	28444	899	300	ORF 18	
JM31	W	28138	28431	293	98		
JM32	C	28452	30095	1643	548	ORF 19	Tegument protein
JM33	C	29590	30642	1052	351	ORF 20	
JM34	W	30641	32311	1670	557	ORF 21	Thymidine kinase
JM35	W	30825	31181	356	119		MHC psoriasis candidate
JM36	C	30863	31111	248	83		Possible transposable element
JM37	C	32279	32608	329	110		
JM38	W	32298	34478	2199	727	ORF 22	Glycoprotein H
JM39	C	33254	33553	299	100		Succinate dehydrogenase
JM40	C	34475	35687	1212	404	ORF 23	EBV BTRF1 homolog
JM41	W	34974	35285	311	104		Alpha-1A adrenergic receptor
JM42	C	35301	35687	386	129	ORF 23	EBV BTRF1 homolog
JM43	C	35737	37938	2201	734	ORF 24	EBV BcRF1 homolog
JM44	C	37346	37612	266	89		
JM45	W	37937	42073	4136	1379	ORF 25	Major capsid protein
JM46	W	39498	39821	323	108		
JM47	C	39842	40282	440	147		
ORF	Strand	Position (nt)		Length		RRV Homolog	Description
		From	To	b.p.	a.a		
JM48	W	40188	40439	251	84		ICHIT protein; mucin
JM49	W	42105	43022	917	306	ORF 26	Minor capsid protein
JM50	W	43047	43871	824	275	ORF 27	EBV BDLF2 homolog
JM51	W	44035	44310	275	92	ORF 28	

JM52	C	44360	45406	1371	349	ORF 29b	Packaging protein (spliced)
JM53	W	45720	46373	653	218	ORF 31	EBV BDLF4 homolog
JM54	C	45836	46195	359	120		Collagen family member; ataxin 7
JM55	W	46310	47695	1385	462	ORF 32	EBV BGLF1 homolog
JM56	W	47676	48686	1010	337	ORF 33	EBV BGLF2 homolog
JM57	C	47768	48136	368	123		Calcium channel
JM58	C	48218	48607	389	130		Protein kinase-like
JM59	C	48604	49587	983	328	ORF 29a	Packaging protein (spliced)
JM60	C	49010	49276	266	89		
JM61	W	49586	50572	986	329	ORF 34	EBV BGLF3
JM62	C	50504	50950	446	149		
JM63	W	50553	51002	449	150	ORF 35	EBV BGLF3.5 homolog
JM64	W	50908	52215	1307	436	ORF 36	Kinase
JM65	W	52196	53638	1442	481	ORF 37	Alkaline exonuclease
JM66	C	53882	55018	1136	379	ORF 39	Glycoprotein M
JM67	W	54536	54850	314	105		Histidyl-tRNA synthetase, ligase
JM68	W	55153	57156	2003	668	ORF 40	Helicase/primase complex component
JM69	C	56124	56474	350	117		Unknown
JM70	C	57153	57968	815	272	ORF 42	EBV BBRF2 homolog
JM71	W	57325	57573	248	83		Chromatin associated protein
JM72	C	57907	59652	1745	582	ORF 43	Capsid protein
JM73	W	59591	61963	2372	791	ORF 44	Helicase/primase complex component
JM74	C	61249	61662	413	138		Transcription factor AFX1, ChCMV UL7
JM75	C	62004	63065	1061	354	ORF 45	EBV BKRF4
JM76	W	62823	63086	263	88		Plexin
JM77	C	63107	63874	767	256	ORF 46	Uracil DNA glucosidase
JM78	C	63850	64341	491	164	ORF 47	Glycoprotein L
JM79	C	64600	65769	1169	390	ORF 48	EBV BRRF2 homolog
JM80	W	65629	65880	251	84		NADH-ubiquinone dehydrogenase chain 8
JM81	W	65963	66208	245	82		
JM82	C	66000	66905	905	302	ORF 49	EBV BRRF1 homolog
JM83	W	66058	66315	257	86		
JM84	W	67096	68640	1544	515	ORF 50	Transactivator
JM85	C	67920	68594	674	225		Chromatin remodeling complex
JM86	W	68957	69469	512	171		BZIP transcription factor
JM87	W	70026	70760	734	245		Glycoprotein R8.1; mucin
JM88	C	70328	70606	278	93		Neurexin 1-alpha
JM89	C	71001	71420	419	124	ORF 52	EBV BLRF2 homolog
JM90	C	71483	71797	314	105	ORF 53	EBV BLRF1 homolog
JM91	W	71873	72745	872	291	ORF 54	DUTPase
JM92	W	72520	72942	422	141		Transducin-like enhancer

ORF	Strand	Position (nt)		Length		RRV Homolog	Description
		From	To	b.p.	a.a		
JM93	C	72806	73438	632	211	ORF 55	EBV BSRF1 homolog
JM94	W	73420	75936	2516	839	ORF 56	DNA replication protein
JM95	C	75447	75722	275	92		Cytochrome oxidase subunit I

ORF	Strand	Position (nt) From	Position (nt) To	Length b.p.	Length a.a	RRV Homolog	Description
JM96	W	76035	76304	269	90		
JM97	W	76162	77484	1322	441	ORF 57	Immediate-early protein
JM98	C	77857	79098	1241	414	R6	VIRF
JM99	W	78411	78656	245	82		
JM100	W	79163	79579	416	139		Ribonuclease III
JM101	C	79269	80510	1241	414	R7	VIRF
JM102	W	79521	79769	248	83		Hepatitis B core protein
JM103	C	80836	81891	1055	352	R8	VIRF
JM104	C	82068	83153	1085	362	R9	VIRF
JM105	W	82206	82613	407	136		RNA polymerase associated factor
JM106	C	83628	84785	1157	386	R10	VIRF
JM107	W	84837	85082	245	82		Transposase
JM108	C	84932	86104	1172	391	R11	VIRF
JM109	W	85290	85550	260	87		
JM110	W	85968	86243	275	92		
JM111	C	86479	87546	1067	356	R12	VIRF
JM112	C	87707	88801	1094	365	R13	VIRF
JM113	C	87763	88023	260	87		
JM114	C	88087	88395	308	103		
JM115	C	89047	90129	1082	361	ORF 58	
JM116	C	90140	91324	1184	395	ORF 59	DNA replication protein
JM117	W	91017	91259	242	81		
JM118	C	91455	92399	944	315	ORF 60	Small ribonucleotide reductase
JM119	C	92381	94747	2366	789	ORF 61	Large ribonucleotide reductase
JM120	C	92929	93345	416	139		
JM121	W	94175	94468	293	98		DNA repair and genetic recombination
JM122	C	94751	95746	995	332	ORF 62	Assembly/DNA maturation protein
JM123	W	95745	98564	2819	940	ORF 63	Tegument protein
JM124	W	98568	104468	5900	1967	ORF 64	Tegument protein
JM125	C	99388	99753	365	122		
JM126	C	99611	100054	443	148		Drug resistance protein
JM127	C	101108	101428	320	107		
JM128	C	102290	102568	278	93		
JM129	C	102857	103150	293	98		
JM130	C	104302	104643	341	114		
JM131	W	104555	105856	1301	434	ORF 64	Tegument protein
JM132	C	105581	106003	422	141		C-myc promoter binding protein
JM133	C	106220	106729	509	170	ORF 65	Capsid protein
JM134	W	106299	106559	260	87		
JM135	C	106733	108079	1346	449	ORF 66	EBV BFRF2 homolog
JM136	W	107289	107696	407	136		
JM137	C	107974	108780	806	269	ORF 67	Tegument protein
JM138	W	108002	108316	314	105		
JM139	C	108796	109056	260	87	ORF 67.5	
JM140	W	109190	110563	1373	458	ORF 68	Glycoprotein
JM141	C	109783	110166	383	128		
JM142	C	110578	110904	326	109		Aldehyde dehydrogenase
JM143	W	110585	111478	893	298	ORF 69	EBV BFLF2 homolog

JM144	W	112447	112698	251	84		RRV ORF RU3-R
JM145	W	113610	114479	869	290		RRV ORF RU4-R
JM146	C	114427	114753	326	109		
JM147	C	115214	115918	704	235		RRV ORF RU13-L; serotonin receptor
JM148	W	115671	115928	257	86		EBV nuclear antigen
JM149	C	115717	115983	266	89		
JM150	W	116366	116650	284	95		Lagopus leucurus gag polyprotein
JM151	C	116918	117442	524	175	ORF 71	FLIP homolog
JM152	C	117501	118265	764	255	ORF 72	Cyclin D homolog
JM153	C	118608	119918	1310	437	ORF 73	Latency-associated nuclear antigen
JM154	W	119237	119617	380	127		
JM155	W	119614	119940	326	109		
JM156	C	119824	120075	251	84		
JM157	W	120484	120744	260	87		
JM158	W	120572	121333	761	254	R15	N-CAM Ox-2 homolog
JM159	C	120689	121186	497	166		CD36; carotenoid uptake
JM160	W	121628	122656	1028	343	ORF 74	IL-8 receptor; G protein coupled receptor
JM161	C	122762	126658	3896	1299	ORF 75	Tegument protein
JM162	C	123126	123398	272	91		
JM163	W	123423	123577	154	85		
JM164	W	123810	124133	323	108		
JM165	W	124395	124790	395	132		K1 glycoprotein HHV-8
JM166	C	124683	125165	482	161		Collagen family member
JM167	W	126063	126371	308	103		Myosin phosphatase
JM168	C	128122	128493	371	124		C-C Chemokine receptor
JM169	C	128789	129046	257	86		
JM170	C	129970	130404	434	145		Unknown
JM171	W	130383	130655	272	91		

The overall G+C content was 51.9% and is distributed evenly throughout the length of the genome. The genes were named from left to right starting at the first

5   ORF on the coding or complementary strand (e.g., 155). The JM prefix precedes each numbered gene to distinguish different viruses' nomenclature (e.g., JM1). The arrangement of JMHV genes is shown in FIG. 1 and was compared with other primate gamma-2 herpesvirus genomes. A phylogenetic analysis was performed using six ORFs from HSV-1, Kaposi's sarcoma-associated herpesvirus (KSHV),

10   human cytomegalovirus (HCMV) and JMHV. The DNA polymerase, helicase, glycoprotein B, major capsid protein, single-stranded DNA binding protein, and uracil N-glycosylase were examined by bootstrap analysis with the maximum parsimony method. Alignments were performed using ClustalW. The KSHV proteins were used as the root for analysis. The phylogenetic analysis revealed that

15   JMHV is a gamma-herpesvirus most closely related to RRV.

JMHV ORFs are arranged collinearly with other gamma-herpesviruses, including RRV and KSHV (Chang et al., *Science* 266:1865-9, 1994; Moore et al., *J Virol* 70:549-58, 1996; Russo et al., *Proc Natl Acad Sci U S A* 93:14862-7, 1996; Searles et al., *J Virol* 73:3040-53, 1999). Most all of the conserved herpesvirus

5 gene blocks are retained in JMHV in both position and orientation, coding all of the necessary enzymes and structural components. Of the 171 ORFs, 81 (47%) are homologous to known RRV proteins. However, the homologous genes are on average 88% identical with a high of 99% and a low of 36%. A protein/protein comparison was done. The percent identity of the two proteins and the scores

10 (except value; calculated based on the size of nr database) for the alignments are shown in Table 2.

Table 2
Similarity between JMHV genes
15 ### with amino acid sequence homology to RRV

JMHV gene	Length (aa)	RRV homolog	Homolog length (aa)	Identity for overlap (%)	Score (except value)
JM2	426	R1	424	82	1845
JM3	194	ORF2	189	94	937
JM4	396	ORF4	646	51	1001
JM5	1133	ORF6	1133	97	5878
JM10	687	ORF7	687	90	3240
JM12	829	ORF8	830	89	3789
JM14	1013	ORF9	1015	93	4982
JM18	417	ORF10	417	91	1997
JM20	410	ORF11	410	97	2128
JM21	208	R2	208	85	915
JM22	334	ORF70	334	93	1637
JM24	121	R3	116	65	378
JM28	188	ORF16	188	76	734
JM29	537	ORF17	537	82	2211
JM30	300	ORF18	300	95	·1527
JM32	548	ORF19	548	97	2796
JM33	351	ORF20	351	91	1700
JM34	557	ORF21	558	87	2532
JM38	727	ORF22	705	73	2638
JM43	734	ORF24	733	90	3477
JM45	1379	ORF25	1379	97	7077
JM49	306	ORF26	306	99	1556
JM50	275	ORF27	270	90	1327
JM51	92	ORF28	92	91	459
JM52	349	ORF29B	349	94	1689
JM53	218	ORF31	218	90	1068
JM55	462	ORF32	465	91	2255
JM56	337	ORF33	337	91	1630

JM61	329	ORF34	329	92	1612
JM63	150	ORF35	150	94	702
JM64	436	ORF36	436	93	2196
JM65	481	ORF37	481	96	2496
JM66	379	ORF39	379	94	1844
JM68	668	ORF40	469	96	2399
JM70	272	ORF42	273	95	1376
JM72	582	ORF43	577	95	2810
JM73	791	ORF44	791	98	4092
JM75	354	ORF45	353	68	1227
JM77	256	ORF46	256	87	1226
JM78	164	ORF47	170	55	440
JM79	390	ORF48	390	92	1759
JM82	302	ORF49	302	99	1595
JM84	515	ORF50	515	92	2492
JM89	124	ORF52	124	79	532
JM90	105	ORF53	105	59	300
JM91	291	ORF54	291	97	1479
JM93	211	ORF55	211	99	1092
JM94	839	ORF56	829	95	4186
JM97	441	ORF57	443	83	1890
JM98	414	R6	416	81	1778
JM101	414	R7	416	90	1978
JM103	352	R8	352	92	1752
JM104	362	R9	254	89	1217
JM106	386	R10	386	86	1814
JM108	391	R11	391	77	1617
JM111	356	R12	356	88	1739
JM112	365	R13	365	84	1697
JM115	361	ORF58	361	74	1319
JM116	395	ORF59	395	94	1937
JM118	315	ORF60	315	98	1589
JMHV gene	Length (aa)	RRV homolog	Homolog length (aa)	Identity for overlap (%)	Score (except value)
JM119	789	ORF61	789	96	4008
JM122	332	ORF62	332	98	1696
JM123	940	ORF63	940	92	4506
JM124	1967	ORF64	2549	92	9299
JM133	170	ORF65	170	66	557
JM135	449	ORF66	449	92	2212
JM137	269	ORF67	225	97	1120
JM139	87	ORF67.5	87	95	431
JM140	458	ORF68	458	94	2361
JM143	298	ORF69	298	97	1520
JM151	175	ORF71	175	91	836
JM152	255	ORF72	255	76	967
JM153	437	ORF73	449	36	162
JM158	254	R15	254	88	1190
JM160	343	ORF74	343	78	1387
JM161	1299	ORF75	1299	90	6241

Unique to JMHV are numerous small ORFs that have low homology to enzymes or structural components found in nervous tissue. Many of these putative

proteins are less than 100 amino acids, which is less than what was reported in the
characterization of RRV (Searles et al., *supra*). These potential ORFs are unique to
JMHV, as analysis of the RRV genome for ORFs encoding proteins of 80 amino
acids or more failed to identify similar ORFs. From this analysis it was determined
5   that these small ORFs are specific to JMHV and includes proteins such as myosin
XV (JM25), myosin IA (JM26), ataxin 7 (JM54), chromatin associated protein
(JM71), chromatin remodeling complex (JM85) and Neurexin 1-alpha (JM88) (Del-
Favero et al., *Hum Mol Genet* 7:177-86, 1998; Liang et al., *Genomics* 61:243-58,
1999; Patzke and Ernsberger, *Mol Cell Neurosci* 15:561-72, 2000). Thus, these
10   proteins could be involved with molecular mimicry or epitope spread leading to the
MS-like disease observed in the Japanese macaque.

The sequence of the JMHV ORFs are provided in Table 3.

Table 3. ORF sequences

JMHV ORF	SEQUENCE	SEQUENCE IDENTIFIER
JM 1	MRWAWFSPFLSHQLGVSNHAPSPGPTSAPLPIPLLPVPSPASMLPAP TALSVRSPRATCRADLGRLPGGPGEGSGPVSSCGPATPSHAAGRLPH YYQP	SEQ ID NO: 2
JM 2	MFVLLIFILLQPASLELLPAKLTAVPTWCPPHPGDTYLLTCRGTSTA RDQRSTQWFRNNTLMHGSNFYGRLVSVTPNSTISDWYACQTKTTTRS NSIDFRVRSSRLTLQERCSSYGYSNANNTRVLRCYSGGNVTLRNVVF HLNGTAVINGTTTDIYTFVLTEKTGGTYYCSAFIGTEKLYSQKINVF FTSFTFKHTDNVQNGSEFNKTEQIQQTANVQHTANYVVFSVPVFSIG VLTGIAISLIMCWLFTLRCNKNSESSNNRHAHQTSYIQPSHNQHSHT SESTTHTYRNDHQEESIEELPNQHTRKTNSCQTVLLEVKNVAFDGPQ GNLHNTNDEVMEQYDDVVVENIEQTSYDNNIEQMDYSDIIRPNFNYY SGLILEEVDEVFYNELANQYHGLILENLDHDEYNHLNKLNMIEQYDW LE	SEQ ID NO: 3
JM 3	MDITVNCIVAVDKQLGIGKNGTMPWPYLKNEMMYFQKMTSTPSVIGE KNVVIMGKRTWFSIPEKKRPLANRINIILSRELREPPKGAHFLARTL DDAFNFYRQYKLTKQLNTVWVIGGKSVYESVLNYECSLKLYITRIME SFDCDVFFPSINFTEYTMLSELPGKDTNFEENGIKYKFQVYEKRLIN KAVTQ	SEQ ID NO: 4
JM 4	MRLIMFWFPVTVCFVCHFILVNAQNETNVTCDKPNFDRFMVAMEKKE KYVLGDKVELTCRPGYTLQGKVYVQCLQSGMWTTPNAECHRKKCTNY GDILNGQVIVPDSDNAFKFGTNITYKCNTGYLLLGSMVRTCLLTGNS NTVNWQPAAPTCEIEKCKKQPDIENGKYYPVQDFYNYLETITFTCNK DFSLIGNTTTTCMTNGTWSSPVPKCEQITCSAPNIEHGTLLVGSSRV YKHGQSITIGCENGFTLNGHKMCTCEYSSWNPPLPTCVPINKTVPTP SEVPSPGTNKQERPTPENPKSHESETTTETPKTGTHKSETPSKKIPN PETHKPTTPKSGTSEQTTNRPSKAPSQNPPMEPPMSKWKRHVVLVLF ASVASLLFVLVTLYCCFLK	SEQ ID NO: 5
JM 5	MASKGNAGQPLEDNQGSRAPIGACGYVYAYSKQDFPFAEASILGNRP SGSGVFSLPILYGLTVEHEFPLTVKAAHKKVDTTTLAVKVTCFHREV IVFHNANLFRPVFEGTGLNELCEEARALFGYTQFIEPGPPHGIWNPL ECPQLPDKDEMFLGVVVTEGFKERLWRGCLVPAVFQTQQVQIAGRQA	SEQ ID NO: 6

	FKVPLYDEDLFAPHGHRMPRFYHKDVSAYLYNSLFTSIAQALRLKDV TAVIHATEKQFMQDHYKIAKIVQAKQFSTTLPKTADGSSHMIVDSVV AELALSYGCMFLECPQDACELLNYDSWPIFDGCDSSEDRVNALERWS AEQAVHVAGQLFAANSVLYLTRVQKQAPRGQKGDVNVYNSFFLQHGL GFLNEATIKENGSEAFKGVPSNALDGSSFTPYHLAYAASFSPHLLAK LCYYMQFLQHHKSSTNQTFNIVHYVGTAANSEMCTLCHGDTPGTCLN TLFYRLKDRFPAVTTPQRRDPYVVTGTAGTFNDLEILGNFASFRDRE EDGNPADEHPKYTYWQLCQTVTEKLSAIGITEDQDNHVNLITNIQSF LRVFKGIDSVVDGEVMKFINSMIKNNFNFREHVKSVHHILQFCCNVY WQAPCAVFLNLYYKSLLWIIQDICLPYCMIYEQDNPAMGILPSEWLK MHFQTLWTNFKAACLDRGVLTGCELKIVHRDMFCDFFDTDAGSNGLL APFKMQVRIARAMMVVPKSIKIKNRIIFSNTAGSEAVQSGFVKPTGT RDTYVVAGPYMKFLNSLHRALFPNTKTAALYLWHKISQTNKTPVLKD VPDDELAELVSYVKTNSLAFEETNVLDVVPDSLMSYARIKLNGAILR ACGQIQFYATTLHCLTPVLQTIDAEEYPHVLGSAAIATPVAYLSEIR GRTALTVQTTARQPVAATGRLRPVITVPMVVNKYTGVNGNNNVFHCG NLGYFAGRGVDRNLWPESSPFKKTGVSAMLRKRHVMMTPIVDRLIKR AAGQTISTFEAESVKRSVQALLEDKDNPNLLKSVILELIRHLGKGCQ DLSSEDVQYYLGDYCMLTDEVLFTLDNIAQSGVPWTFEDAGALIEDR QNTDDLQFVDSDDIATASCQPPEEQLPTPSAGALLAGKKRKINVLLS DLDL	
JM 6	MVLHELFFCGVDDRRHVFESQGLGDTGKKGVVEVRANVFMVKPRHPM PVRCEQVFVVQRHFERLTPGDLHLLGLKHCGNETAPPQSLLKPFRHD NAKEHLILVR	SEQ ID NO: 7
JM 7	MAPFSLILAYDMRESGTTSSTFVSSNARLLVLTYDTSSASSSSGTSF RTGVLLVWEILCHRYSAAVLVFGNSARWSEFRNFMYGPATT	SEQ ID NO: 8
JM 8	MQRCGVELNLTARPQNGPVQFNPRVRHEGIRDHVQHVRFLEREAVGF DVRHQLRQLVVRDVFQDWGFVGLGDFVPQVQRGGLGVWE	SEQ ID NO: 9
JM 9	MFLARCSTSSDRLDVSTEFCLRSSGRRSRFRFSICVFVFRMREPSIL RGSAKTTRLRSTARADSCAYKAASSLAIVVRRPRFS	SEQ ID NO: 10
JM 10	MARELAALYAQLSALAVDLSLVVFADPRSIDGSRILKTKTQIENLNR DLLPLLRKQNSVETSSLSLEVEHLAKNIEDKLGELERSLRQRYSSRE HFETLHLRPECHYHATVTFEFYGGGLIDVNMCLINDVELLCKRLGSV FYCIGANEALSGLDRVLAFLSTLRGISPIPHPDLYVTSVPCVQCLRE IELVPNQGSSLLAVLADRHCDHLCKKVRAEPIHGLFETELSQLGLKV AKGSDATQHGVRSSADQLRESSLAAIQDHNIFKRVSASIMELSNLIY WNAGQTGLQTGTENECSQMAKLLTHEAEMHEHRALITPKQSAAHFYD CFRPDPIESLFCGGLFNSIDDTINALSRDCSVTFFQQANYTNVMRKQ NELFTRLNSILCQGSAGSQKPATPSEPRTATVAATAASDVIKDAQYR KEQYMKKVARDGFKKLTECLQTQSAVLANALCMRVWGGVAYGEASEL VNHFLLRRRFVALPWEARCRSNQILFENSKYIKNSLYSQRLSREHVE IITLQFYGLITGPLTRQSDLFPGPANVVLAQCFEAAGMLPHHKMLVS EMIWPQIQPKDWIDQTFNRFYQLPEGDLNAVQKSAWCFIRELVLSVA LYNRTWEKTLRIFSLAREKPSISDLDVKSLTPGLYLTYEQNTPLVLI SQNTGWIFKDLYALLYHHLQLSDGHDDN	SEQ ID NO: 11
JM 11	MWGTIFFLNTIRMPSWCVLSSVPGHVFSRLNLKSSPVAEALHTRNLN ASALGGFSGGVGVDGPGVDFAVVVTPFGVVTFSPTAAPIAIITTHAR SRRRVRLVIIMAV	SEQ ID NO: 12
JM 12	MMITNRTRRLLRAWVVIIAIGAAVGENVTTPKGVTTTAKSTPGPSTP TPPENPPRAEAFKFRVCSASATGELFRFNLEKTCPGTEDKTHQEGIL MVFKKNIVPHIFKVRRYRKVATSVTVYRGWTETAVTGKQEVIRPVPQ YEINHMDTTYQCFSSMRVNVNGIENTYTDRDFTNQTVFLQPVEGLTD NIQRYFSQPVLYTTPGWFPGIYRVRTTVNCEIVDMIARSAEPYSYFV TALGDTVEVSPFCLNDSTCSVADKAENGLGVRVLTNYTIVDFATRTP TTETRVFADSGEYTVSWKAEDPKSAVCALTLWKTFPRAIQTTHEASY HFVANDVTATFTSPLSEVANFTGTYSCLDNVIQKTLNATIKKLSDTH AANGSAQYYETEGGLFLLWQPLTQLSLVDEMRGLNDTTPAPPTTSTA SRVRRSVDTNSQTAEDLAAPQLQFAYDKLRASINKVLEELSRAWCRE QVRDTYMWYELSKINPTSVMTAIYGRPVSAKFVGDAISVTDCVTVDQ	SEQ ID NO: 13

	GSVSIHKSLRTSTPGICYSRPPVTFRFLNSTTLFKGQLGPRNEIILT DNQVEACKETCEHYFIASNVTYYYKDYVFVKKINTSEISTLGTFIAL NLSFIENIDFRVIELYSRAEKKLSGSVFDIETMFREYNYYTQRLAGL REDLDNTIDLNRDRLARDLSDIVADLGDVGRTVVNVASSVITLFGSI VSGFINFIKSPFGGMLMILVIVAVILIVFALNRRTNAIAQAPIRMIY PDIDKMQPSGGKVDQEQIKNILAGMHQLQQEERRRLDEKQRSAPSLF RRASDGLKRRFRGYKPLENEEAQEYEMNK	
JM 13	MGAWAMALVRRFSANTIRMTATITRIMSMPPNGLFIKLMNPLTIDPN RVITLLATLTTVRPTSPRSATISDRSRARRSRFRSIVLSRSSRSPAS RCV	SEQ ID NO: 14
JM 14	MDFFNPYLGPRGPRPPSHKCTDAPAPAGAVQPPPDVCRLIPACLRTP GAGGMIPVTIPFPPTYFENGARGDVLLAHERSMWTARGQRPVVPDPQ DQSITFHAYDVVETTYAADRCAEVPSRFQTDIIPSGTVLKLLGRTEN GTSVCVNVFRQQVYFYAKVPAGVNVTHVLQQALKNTAGRAACGFSTR RVTKKILKTYDVAEHPVTEITLSSGSMLSTLSDRLVACGCEVFESNV DAVRRFVLDHGFTTFGWYSCARATPRLAARDARTALEFDCSWEDLSV QADRSDWPPYRIVAFDIECMGEAGFPCATRDGDAVIQISCVFYTTRE GAPNPPNILFSVGTCDPIPDTDVLEFPSEYDMLVSFFAMLRDFEVDF LTGYNISNFDLPYLITRASQVYNLRLNEYTKIKTGSIFEVHEPRGGG GGFMRSVSKIKIAGIVPIDMYQVCREKLSLSDYKLDTVARQCLGGKK EDVSYKDIPPLFRSGPGGRAKVGSYCVMDSVLVMDLLKMFMIHVEIS EIAKLAKIQARRVLTDGQQLRVFSCLLEAAARDNFILPVPTPEGQGG YQGATVINPIPGFYDEPVLVVDFASLYPSIIQAHNLCYSTMIHGRDL HLHPNLTPDDYETFVLSGGPVHFVKKHKRESLLGRLLTVWLEKRRAI RRTLAACDDPSLKTILDKQQLAIKVTCNAVYGFTGVASGLLPCINIA ETVTLRGRTMLEMSKSYVEALTTDNLRTRLGREVTACHGARFRVVYG DTDSLFIACDGYSAEAVSAFCDDLAARITADLFPPPIKLEAEKTFKC LLLLTKKRYIGVLLNDKMVMKGVDLIRKTACKFVQERCRSILDLVLH NQEVKAAARLLCKRPPHAVYEEGLPAGFIKIVEVLNASYVDLRNSVV PIEQLTFSTELSRPVCDYKTTNLPHLAVYQKLASRCEELPQVHDRIP YVFVDAPGALKSDLAEHPDYVKQHQIPVAVDLYFDKLVHGAANILQC LFGNNADTTVAILYNFLNVPYKLFS	SEQ ID NO: 15
JM 15	MLRDVVRFENFFGYSSGREAARGPAGGVLEGLLEDVGDVDAGWDLRV EIYLLTEHVHAHAGAVLGSPQELEHGSARNNVRLEAARYLGAPVRRV RRFNDVVRVKRNGLVLGVRDDWPLAARRPHGPFVGEQHVSARAVFKV RRRERDRDRDHPACPRRSEAGGNEPADVWWRLNGAGGGGRIGAFV	SEQ ID NO: 16
JM 16	MHRSAAQHERLVVVRRQVGVQVQVSSVYHGGVAQVVRLDDAWVQAGK IDHQDRLVVKPRDGVNHRRALITPLSLGRWDREDKVIPGRGLQQAGE HAKLLAVR	SEQ ID NO: 17
JM 17	MPLHPGPGAPQSGGQGGGAAVVQATAARGIRGGVAGGLYKNCGGPQR ELCGPSKQRRAHRAVNVLDRAQPPRLRLQDHQPAPPGGVPEAGEQVR GAAPGAR	SEQ ID NO: 18
JM 18	MLVNELSMVLGDWEVTFHRGKFSFVNLARLQTFKGHGGYAKIRLPFS LDQLLHQHFAFGLVTRLNELPPFSDCVALIAPRDSGGDADAARVAPG FVLDSSRPLTVWVNANGRHTVRFCLLFLKPIDLERAVTYVFGENGGA RSEGAPKPTCNTESLPGGPLRVSGEASQTSPHSFVAYFPTADPVACL SLLRLQVRPFSDDAAHRDARISPKYVTFSNAGGNVCKASVHTLSPSR CKTAQMEIIYAPGDPNAEIVLGQSGPVLPTHTGGRVLGVYADAEKTI QPGSSAEVRVQLIFQQGAAARGDLAFLVAGVAPEPLFIVTPTLLLSG CTTHLRLFNPNGTPTTIKRDTLVAAAPCPVVRVSSADDAPRDLVAS PDTGALSIDAFTIPVGLPGVVSAECHVSMRDNGVHERMSH	SEQ ID NO: 19
JM 19	MESAPVSGDATRSRGASSAELTRTTGQGAAAATRVSLFIVVGVPLGL NRRRCVVQPESKSVGVTMNRGSGATPATRNARSPRAAAPCWKIN	SEQ ID NO: 20
JM 20	MGTPVRFFRGEWQTSSLVDNGTPRYSSLVWAATIHDGYLTLVNRSEL CVTERSPCLPACPSIGRLVGKRFPGFAFASATLGDRGTRTVFYAFGH RDNPLDIVPAVVERADRELVLRVHAPRTTRVSRYGLKIFVAIVTVVR PPGVFLHFPQDRVPIALTDACSQEGSRLTSEEPWIKIQGFPVLSDET AHPFLLTQKTKPFTERKFCRLIMDDNQLSAVNTVYLGKQHVRVTVTR PPETIVTDGPVTATLSLTGNAPIAFRHNPYFELPWSSTTAIFTPVVY	SEQ ID NO: 21

	VGLTVCIPPNCSKFVRYGNTYVSAFNRKLTAIISNHAHDGGFRIQDC EWPPNREIEILVTNVTQAPVYVSTGTQLGRAIFVFAPRFGGPAKLRQ LLGHRSRALELPGGVTVDSQKLCRFETMYLFST	
JM 21	MFPVWFVLFYLSCWAASPTLAPPPTAAGINVLPQWAGNRASLDRTRG RLSELGLNIQRWFVYLCYHSTLCRVREYPRIMSFINFPILMSNVECQ RREFRGAECMNAMVRGLRAYESYLTRSKMLLDDAPGNAGAAAIGSAV TVVLSALNSLIEELPVDNKIGGVESNDKIVRALAEQSPGDVILSAFR LLEYLQMFLRDGRRAIAMM	SEQ ID NO: 22
JM 22	MIVLVHLGICYVKKIIPACLSGIAAVRCRVSRGSEVAAARAPDGRGE HGELQYLAHLDLIIRHGVQRDDRTGVGTRSVFGLQARYNLRDEFPLL TTKRVFWRGVVEELLWFIRGSTDSTELSRRGVKIWDAHGSRAFLAAQ GFGDRREGDLGPVYGFQWRHFGAEYRGADADYEGQGVDQLRYVVDLI VRRPHDRRIVMCAWNPADLARMALPPCHVLCQFYVARGELSCQLYQR SADMGLGVPFNIASYALLTYLIAHVTGLTPGDFVHTLGDAHVYNNHV GPLLLQLGRTPRPFPRLKILRKVTRLEDFTRADLSLEGYDPHPHIEM EMAV	SEQ ID NO: 23
JM 23	MCLHGGASTMTLKINVFCGSCTMRVWLMNAGGDSGGDAGGDSGGDAG GDSGGDAGGDSGGDAGGDSGGDAGGDSGGDAGEGPRGFTTR	SEQ ID NO: 24
JM 24	MRVLVIGAFFAVFACVVDYAFPMGSMSGPAPEVCCLGYINKLPPSGA VALYYYTSSQCTLDAVILETHRGQKLCANPGDDGVRKLLQKVDNRPK RNKGRRTRRSLLDDASDEGLESGSGF	SEQ ID NO: 25
JM 25	MRRVCLGGGDFPFIAGTGPLLVLEIPFSTGSLLRRKAVYLFGESPFF RTPGATVVRHARFGTRDATSGREARAPGGWPRLVSVEADPGRGY	SEQ ID NO: 26
JM 26	MLFLVAIGDIFRCPPNDPVRRGFFGSFGGHRKMFPRARRATVETIFS DPLVTPEPAPPRGAPCLGAEQSVLVRTPNAGLAVPTPARKTRGTPAG FYAITLCYFGVGAPRCPC	SEQ ID NO: 27
JM 27	MSGVSVTRGAEAAGGGVGKNSGRRARVSVMTRLDGGHLAAGQRREHR ERPAGGAARDRAPRSVKMADRRRRLGAADVNHGGEERRWSGYTSITE GRAGWQII	SEQ ID NO: 28
JM 28	MAAIQGPPPLPEEENENSLPDDVYAIEGIFLYCGLGQAEYLHHPVFS PIKEFISSFLKDSARLYERLLRHTDYRSLRGLNAIGQGMLHINTDGR HNWGRALAVLGLGAYVVDKIRDDERLLTFAIAVLPVYAYEALESQWF RSHGGWEGLRNYCERILRHRRNARRHMCYGVAAGLLALVALFAIRR	SEQ ID NO: 29
JM 29	MTSVYVGGYVDVVSLPKIEKDLYLEPSIVATLLPYTNPLPINIEHVP EAHVGHTLGLFQVTHGIFCLGKLTSPDFLALASRLAGDSRAAQIQLN PMPRDPLLEMLHTWLPELSLSSLHPEELQDPNHPPAFQHVSLCALGR RRGSIAVYGPDPTWVVSKFDSLTRDEAGKITSKCLDLCERQVTPPEF AAPLETLMAKAIDAGFIRDRTDLLKTDKGVARVARSTYLKASQSPSS QHGGNRDTQTMSALPDDNITIPKSTFLTMVQSSLDHMRNQGQRAYVS APPSMPATAAYPSWIPPPELTVPSYAPPVAPPFPFQSAFAPQPSPYA ATYYSPTYGYAQAPSRHQKRKRDVELSDEPVFPGEEVGIHKDVMALS KNILDIQADLRDLKRAASQTSGEKDTQRPQPPPVQFSWPQTYASAP YLAYQPQWYPGTDTHLHASQPYQIAQGIQQTQPPPPQPASHHAGLAT QPVAPAPAAQESAMSNAVPSASAPRAGACPPLDSDCGQSARAPVEAS VQPAPVSQIQKMFCEELLK	SEQ ID NO: 30
JM 30	MFIGRGFVYGSRVATIEGSKYRSFSIFGRLTTSTYPPTYTEVMLGRC LREPKEMSAGLRGLMWRVIRCENLNTFLPGELRFLHLVLCEMYNYGL NVYLLKEAIANTGTRDDIVLGRKVPVEFWKIIYDGLREMGVSDATLL SETKRGALWLYFNGRPCLLKGLGDYVFCRLGLSHSVRVVPENLTDGN YLYNLGSVIPCRLLVALSYCLAFWGHADHEPWVRLFAGKIFILYLII SGHIMPRKSILEQVGTSGYGGFVEAVCRDVRAVHGIPAWDFAAAAPA LTSRQTDYLFAFNNSVV	SEQ ID NO: 31
JM 31	MSPASGAELLLGVLGARRPRALGQVVRRQDFYTVLNNIRPHYATKVN LRTGGNVRVRWLCRGCVSRRSRGPRHSGVGFCGSGSGVNVSTDGLPV CVQ	SEQ ID NO: 32
JM 32	MRTSEKCCMRYPRKPARQITATFWAPHPNNVLFIHKPSLIEERRNAF VMRNQQLALRVHTLRKNLLRLELDNVLQTHQRETEMVMRDLDTIQNM VGDLRSPTRETADTQTSINPRPKIAPQTHGDAFVVTIAPGDPGFTVN QDLRLELLPSLYMNQNQWLPQYGPWYSSLTDNAMQRRVFPRDLRGTT	SEQ ID NO: 33

	NFQNSTSLKLMSAVISTAASITQDFYADVRNVSDTQAALCLLNGYYC HRTGTPLPPTRDGLWDNLGTKLATLISHLKQNTKGLGFEFTYSNPKQ RASLAPLNKETKYSADFFTNHVIYATLAQSGLLPGSKNPGTGQPPGP DLVYILATTLFSEDVPPFQAYQWNLRAGLSALGCLVLVYVLLELAQI TPRSPHRRLNLASLLGGRFSKVEDPSGSKQYLKKGQLFDFLTENYIS PLLSRAPDAPTSFLFPGAYLTALEAKAISHLKHTRPFVNLTGSRFNE IFDILNQKLTFRDAGSLIQAQTSLRLTAEEGLAAILSHPSPPGLTHE IMKSQFGVYDDYDKVYFLVLGYLPVATSVV	
JM 33	MTVANQCKHAATLEALPASRKRAGIRAHLAVYRRLIKHRSLDDILKF LSIRPTREATKDVKFRIFFEVTLGRRIADCVLTVDSEHQKTCYVIEL KTCLSAAVFPGNAIKISQRWQGLHQLTDSVAYIGRAAPRGHENWSVR PWLLFKNQKTLKTIHTESSAFPPTFINTTSVALNGFFSQWEDAHVRK MLYEISTKTSAANYRNFLGPTSKQRSVHSQTIADRRKKKRVCDAKST AGAKGSHAAKKPAPSRARQRAADAPTGNRNGHARPRHNSKHGRGSAV PDQGNRRYPNVNKPTTQNRPSDTWRRVCCHDSPRRPGLHGKPGSPSG APAQPVHEPKPMAATIRSVVQ	SEQ ID NO: 34
JM 34	MAEGGSGFGDELVRQMRDRKPRWDESSDDTDDVDTESTDLEYDDVFP VVDTHGLTSPGSQNYDVPTSPSGTPWELLHPDALYAQPRCPPKRAAV PGGGARPKVSAFSARLQYVGRQSFGDRETRQLTGAQFSSESEHEYAE IPERTTRPVESGDKRHFTSGRRGGISGPSSSKPSNGAGLTRKTKTSL SVSLKNLLRIKDDDVKVDVPRPVTVPVHLMQPHPMTEYRNAFLIYLE GVMGVGKTTLLNSMTGMVPQENVLSCPEPMKFWTCVYSNCLKEQRSI VKQGTHGKSITSARVYACQSKFALPFRATAAGIGRNLQPWLVGNGST KPANWIVFDRHLLSATVVFPLVHVKYNRLTPDHLFQILSLFSAHDGD VVVLLTLNSSEAHRRIQSRGRKEEKGITQNYLRQVAWAYHAVFCTWV MMQYLTPEQMVQLCVQTVSIEDICNMNSRLTHRFLTLTKLHEQSMIP MVVEMLAAVKEHVTLMEVCLGLFKELRKLQILIVDAGEHLDDTCGLW GNIYGQVMSNEAIKPRAVNWPALESYIQTLTSLESNAAN	SEQ ID NO: 35
JM 35	MTYPRLRPERRGNYCTRTLCMRSRGAHLKGRPCRAVVRGPRCPRSRL DFNMLDDRVLGIERRGSLPGPSFLPRASTNMRKYRSVLHARLKAGTR DILPLGVGVEFRDPRRQNLVTVRG	SEQ ID NO: 36
JM 36	MSLVPAFNRACSTLRYFRIFVLALGRKLGPGKLPRLSIPKTLSSNIL KSSRERGHLGPRTTARHGRPFRWAPRLRIQSVRVQ	SEQ ID NO: 37
JM 37	MFNFKIPFLFCNVSCNVSRIFELAQASCITREVNTSLTFFQLIRYRV LLNSSSTVDISLLTGVVVAGVKRTISSPGTFSSLYSYPLITENVITN KHKPWLIGCIAFQAG	SEQ ID NO: 38
JM 38	MQPINHGLCLLVITFSVINGYEYNEENVPGLEIVLFTPATTTPVKSD ISTVELEFNRTRYRINWKNVSEVLTSRVIQDAWASSKILETLQETLQ KRKGILKLNMAYVSNKEINFCKSFSSSEIINITSDFNYSSLPGFLGS FDVINHELTHGVLVSKRELFTNALDIMGLFYAIKLNAETFKITFDES KVIISGIMTADWILVSIANSSSEVNGQCVALLFGDPEKFPPLKGYVS YRDLVVVRNDNYAIAVIAPMSHGTMGLNFLPQNLTDIFFSILNSPLK VINYLKGKLFELESKGACQNPSNEQNILSLFFEVTAIHFLYVRNLNK EEPVNVGCVVKHVAALKSLERLFKLCFPAFELHSLNLWTLSHLAASQ IANLPPNNVMSLTMDEQEVVFSMFKLADNNNVNEIILNEIINISDQM YTMYSDIYQLSNTYRQTVMDIYEVLTTVSLTNVGARAVYPYILFTSM CNNVEISYMINQISKPDDITIFRVFSPCFLSLRFDLDENKLRSDAPQ TSKRTGSELAQGASGFWRLLHAFHATRINEFSVINCTRLAWKQVTAL MPLTNITYVISSVRPDHARVYEVSEVFLNSAMFVSAVYPNCSHFTPP GTALHIPILYNFSAPRIGCPLCDSIVLSYDENQGLQTMMYVSNPQVQ ANLFSPYSPFFDNDNFHIHYLWLMNNGTVVEIRGLYRRHALSAIAFV FAFIGTMSALYFLFKLFSILA	SEQ ID NO: 39
JM 39	MFIISFKMISFTLLLSASLNIENTTSCSSIVNDITLFGGKLAICDAA RCDNVHKLSECNSNAGKHNLNNLSKLFKAATCFTTHPTFTGSSLFKF LTYKK	SEQ ID NO: 40
JM 40	MGSRQPQIGESPITAFNTVTIMQRANNSIMFLPNLKLKPIQHLFLKH VLLQRLGLENILFHFKMLYANTCKAAAPYQREYFESMLSRVKQRLED MVFCLNSIESHNFQKDFKVTSRAPQQLLTATDKYFLMFPPQNRDLAI QVGAEVIESICDGTPLFEVLANLNPRVTIQKETGNNLLKFYALLTV	SEQ ID NO: 41

JM 41	MIVTVLNAVIGLSPICGWREPMAKNMSASKQSDCTSESLVAGGCLRM DRSFLSSDVKGALHKVGGAFGSYSCVVFASSFMVICLLFVRVTGGVL TVTWTENGL	SEQ ID NO: 42
JM 42	MIKIPDLKARLVGGAVQLSNGEYVCHVVYSSALAAMVGLPGPAVPLP LLFKKFGTIYSNMMPLYAPKRPELSMLRIMVSPHPYALNSCLCVGTD EGERGVSLFRDPVIRSSDFDDTPITVRLKISDRE	SEQ ID NO: 43
JM 43	MMLLQGPVLLPACPATATADTPSPANSDFKTQLAIFCCLATNNEILE NVSLEVLDRAMETETTFYACRALRRLVLGEGLYPFIHRQGGIVGKTG NEYAGPGLIIDDAIGCTFSHIETHTFLPTVFTYELSDTVWVQRDERI LRSLYCSPLMVCGVNYQSMFRILCRYLQIWEFEECFAAFTRTLPEHL IGTCYQNYFKLLEPFKTLTLARCPPPCAKLHLNYLKFNILGFTSDWI SHPELHRVQTVIIYNIESNPVLLKNLSKQNKFQDIRVASELIIDYQN IVNQSLGVNLQVKINKKDPGKKPYKVVVVTPKSTYYLTFPPEVPIFR VAMCMSVAEHVCHSCDRLYPNTEFLGPGETPRVLEAMFSRIQYAPKD RDHNFIFDANQNPDRHKQVHHDHQTEPLPDMFDPVKHLSLHNFKISV FNTNMVINTKITCRSLTGTFESIIDIPRLTNNFVMKKFSVKEPSFTV SVFYSDNLCNGAAINVNISGDMLHFMFAMGNLRCFLPVKHIFPVSIA NWNSTLDLHGLENQYIVRRGRRDVFWTTNFPSVVSSKDGCNVSWFKA ATATISKIYGRPLLKKLSDELDPILSVPYARIDQVKNTIFTTLETRN KAQIQTLHKRFIECLVECCSFLRLDLGALNRAARLGAFDFSKRIISH TKSKHECAILGYKKCNLIPKIYVRSKKIRLDELGRNANFMSFIATTG HAFSNLKPQVIRHTIRRLGLHWRHKAKI	SEQ ID NO: 44
JM 44	MYIFPHRNAYVFTHRLHLRTVRHGLGSTRRTNPTVPVLFAINGMWRK LSKHVSNSLSLPSNMGIRGMLCRLHAYTAGTSDRHVLSELL	SEQ ID NO: 45
JM 45	MEAALEVRPFPYMATEANLLRQMKESAASGLFKSFQLLLGKDAREGG VQFEGLLGVYTNVIQFVKFLETSLAVACVNTEFKDLKRMTDGKIQFK VSVPTIAYGDGRRPTKQKQYIIMKACNKHHIGAEIELSTDDIELLFI DRETPLDYTEYAGAVKTITASLQFGVDALERGLVDTVLNVKLRSAPP MFILKTLSDPVYTERGLKKAVKSDMVSMFKSYLMDNSFFLDKSDIAV KGKQYVLSVLSDMVGAVCHETVFKGTNTYLSASGEPIAGVMETTENV MRKLLNMLGQVDGGMSGPASYANYVVRGENLVTAVTYGRVMRTFDQF MKRIVDRPNAQPNVDDDRDAVADGQDSLAKTPIAAAVIQIGDKLVAL ESLQRMYNETQFPFPLNRRMHYTYFFPIGLHMPRPQYSTSATIKGVE NPAEQSVETWIVNKNNVLLSFNYQNALKSICHPRMHNPIPCGQALGQ AFPDPGHVHRYGQKSEHPPNMNLYGLVYNYYQGKNVAHVPDIALKAT MTTDELLHPTSHETLRLEVHPMFDFFVHQQPGAQAAYRATHRTMVGN IPQPLAPNEFQNSRGLQFDRAAAVAHVLDQSTMEIIQDTAFDTSYPL LCYVIECLVHGQEDKFLINSPLIALTIETYWNNAGKLAFINSFPMLR FICVHLGNGSISKDVYAHYRKVFGELVVLQQALSKIAGHEVVGRRPA SELINCLQDPNLLPPFAYNDVFTNLLRQSSRHPMVLIGDEGYETEND RDTYINVRGKMEDLVGDMVNIYETRNNADHDGRHVLDVGPFNENEQH MAVLEKLFYYVVLPACANGHVCGMGVDFDNVALALTYNGPVFADVVN PDDEILDHLENGTLREMLEASDIHPTVDMIRTLCTSFLTCPFVTQAS RVVTQRDPAQLLTTHDDGRYVSQTVLVNGFAAFAIADRSRDVAETMF YPVPFTKLYSDPLVAATLHPLVANYVTRLPAQRVPVAFNVPPALMAE YEEWHKSPILAYANTCPITPTSLSTLTSMHMKLSAPGFICHAKHKIH PGFAMTAVRTDEVLAENLLFSARASTSMFLGQPSVMRREVRADAVTF EVNHELASLDMALGYSSTITPAHVAAITSDMGVHCQDLFLMFPGDSY QDRTLNDYVKQKAGCQRFGGPGQIREPVAYVAGVPHSDNIPGLSHGQ LATCEIVLTPVTADVTYFQTPNSPRGRASCVISCDAYNNESAERLLF DHSIPDSAYEYRTTVNPWASQQGSLGDVLYNSTSRQVAVPGMYSPCR QFFHKDAILRNNRGLNTLVTEYAARLTGTPATSATDLQYVVVNGTDV FLEQPCQFLQEAFPTLAASHRALLDEYMSNKLTHAPVHMGHYMIEEV APMKRLLKIGNKVAY	SEQ ID NO: 46
JM 46	MSCCTRPRTRRFVWRFIRCLIFLFISSQVRKPRIGLPTGLWWVTFRN HWRPTSFKTAEACSLTERRPWLTCWTSQPWKLSKIRRLTRHTHCFVM SLNASSTDRKTNF	SEQ ID NO: 47
JM 47	MIRVVSGFVNVNHVTDEVLHFSSDVNVRIPVIFRFVPLVSYEYHRVP RGLPKQVGKNVIVSKGRQKIGVLKTVNQLGRWPASHHLVASNFRERL	SEQ ID NO: 48

	LQNNELAKNFSVMGVHVLRNTTVAQVNADKSQHREAVNKRQFSGVVP VGFNG	
JM 48	MTGIRTLTSEEKWRTSSVTWLTFTKPETTRIMTAATSLTSVPLTKTN STWRCWKSSFITWSCQPVPTATSAAWASILTTWPWP	SEQ ID NO: 49
JM 49	MALDKSIVVSVTSRLFADEIANLQSKIGCILPLRDAHRLQNIQALGL GNLCSRDSAVDFIQAYHYLDKCTLAVLEEVGPNSLRLTRIDPMDNYQ IKNAYQPAFHWDNYSELVVIPPVFGRKDATVSLESNGFDVVFPAVVP EPLAQTVLQKLLLYNIYYRVAETTPTDVNLAEVTLYTTNITYMGRNY ALDMDPVGSSSAMRMLDDLSIYLCVLSALIPRGCVRLLTSLVRHNKH ELVEIFEGVVPPEVQALDLNNVSVADDITRMGALMTYLRSLSSIFNL GRRLHVYAFSSDTNTASCWCAYN	SEQ ID NO: 50
JM 50	MSIPKIMTVSRDNEGTVCEVAVDNGRHRAMIYYPKITNSSNERAAQR ADVVKEAFDTETPVDIVKQIVNEGLAISKRNCVRLALYLYFYLQYVC FAILITWQLNPHIDPPGLVFAVNPMGPKHVSKLPHPAIVAVGCGTDA ICKNCSVPDIKTELGVVYHNGSSDSGQSAHYGLALLKAAWLVMGNVC PEPVVRQGAELLGPWNRTAWLDFKSAMAATTFCGSRGVLWSPIHEKN LCRPTWNDVINTSSFFTNESLCPNVPGVSEIVIVLNGDA	SEQ ID NO: 51
JM 51	MTAHTNGVLTTTGVSTSQPESFQISPFFRVITKPPIMGLFFCVAMCI IALVWYVMRRVYCKGRVVADSCRDPRRPAYEMLNVRLRPHGTNP	SEQ ID NO: 52
JM 52	MLQKDAKLIFISSSNSSDKSTSFLLNLKDAHEKMLNVVSYVCPDHKD DFNLQDTVVACPCYRLHIPAYITIDETVRSTTNLFLDGAFSTELMGD AATSAQSMHKIVSDSSLSQLDLCRVESTSQDIQGAMKPFLHVYIDPA YTNNTDASGTGIGAVIAVNHKVIKCILLGVEHFFLRDLTGTAAYQIA SCAAALIRAIVTLHPQILHVNVAVEGNSSQDAGVAIATVLNEICSVP LSFLHHADKNTLIRSPIYMLGPEKAKAFESFIYALNSGTFSASQTVV SHTIKLSFDPVAYLIDQIKAIRCIPLKDGGHTYCAKQKTMSDDVLVA TVMAHYMATNDKFVFKSLE	SEQ ID NO: 53
JM 53	MSFLYHNRCKECQMTRVNSPICQFHNVSSLYQCLDCKRYHVCDGGRD CVIVYTRENLVCDLTGNCVLDNVQDVCSYGPPERRAPDAFIDPLVSH GTRESLKSDILRYFETVGVKSEAYSTVVKNGQLNGIIGRLIDATFNE CLPVMSDGEGGRDLAASIYIHIIISIYSTKTVYDNLLFKCTRNKKYD HIVKTIRAQWMRMVSTGDPSRVNATGCFT	SEQ ID NO: 54
JM 54	MLAARSLPPSPSLITGRHSLNVASINLPMMPFSCPFLTTVEYASDFT PTVSKYLNISLLRLSLVPCDTRGSMNASGARRSGGPYEHTSCTLSKT QFPVKSHTRFSRVYTMTQSRPPSHT	SEQ ID NO: 55
JM 55	MDAHGLNRRSVAGQCDGLFHVILPRGFILANNITCGGRQRFFAHTRF AASERTSKTLYVWGRVFQNTDPGSGDGPSGPWSGLAISLPLFTTNGK FHPFDVVILRAETPGSGSSWTVKFLYMSLIAAYRNAMRGLKDKVSQS TDAAVDGEVHPLTVLKEALVSPDTATRPVSACNPLQMLTGLLQSRVR DDYVTHHRALERPGNVRGQVSAPTRTEMPNGSPSRVRLGFRPPKQAN YPKTWAQARHVFSSRTYYVCVYDNEELDTKWQRQDPRPLSLDWSDPV AYLLEGDLFLGAKQNAFVDSLEKTCRCQNYTIKQFFPVSINRDNDTV DLIKEHFIEACLVIRNQASERSAWVKAALFRNDSNTYWKDVLGLWEH GPHKLGTAIKRPTSEPCNADIDWSWLLCDADITRSINGQSTVCLVVS PALIAWLVLPGGFVIKGRYDLSSEDLMFVASRYGHPAA	SEQ ID NO: 56
JM 56	MATQRRDILKSFLNKECIWLRHPGTSAFVRVYTATTAHSAVFDPPVT SEDAMSHNCLNVMIMLMKPKEFGPCVTVYINGDILDFCATEYVAIRE VPGRADLCLIRFGTLSNAPRSVPIPGPLNPHPRENVPGLTKQEIIYT SQTVPRAQIQDAIKGKAFKQINPFVWFDGGAFWQLFLSVDYMLLCPA LEIVPSLARIVGLLTQCDKSTCKICTLAHVHVNAYRGYTPPDSQGTS PSCPCLISCGARHATDVLVTGHVNLLGLLFDPKVLPKVSRLRLKRNP HPVPIEDAMSGVTAEGTEVLPTSQPWALIRLPDLASRVMLYGCQNLK TICLRSY	SEQ ID NO: 57
JM 57	MASCICALGTVWEVYIISCFVSPGTFSRGCGFNGPGIGTLLGALERV PKRIKHRSALPGTSLMATYSVAQKSRISPFMYTVTHGPNSFGFMSII MTFKQLCDIASSLVTGGSKTAECAVVAV	SEQ ID NO: 58
JM 58	MRAHGCEVGSTSVPSAVTPDMASSIGTGWGFLFKRSLDTLGSTFGSK SRPKRFTCPVTRTSVACLAPHEIRQGHEGEVPCESGGVYPRYALTCT WASVHILHVLLSHCVRRPTILARDGTISRAGQSSI	SEQ ID NO: 59

JM 59	MLLTSYRERLQNNLRAVTDGGCENWFRQPPVIISGNDKTERMAHPCL GVIHAVNAYSSVLDDYLQTYRRLQEPMPPPTLGKPRISSHATLPRLT EELTNYLRQTCCRVRMADAKDQHMEYQSAQRTHEAFLECPVYAELRQ FLANLSSFLNGSYVPGVCCLEPFQQQLIMHTFYFIASIKAPEKTHQL FATFKQHFGLFETTDDVLQTFKQKASVFVIPRRHGKTWIVVAIISVL LSSVENVHVGYVAHQKHVANAVFSEVIATLSRWFPAKNLNIKKENGT IVYASPGRRPSSLMCATCFNKNVSRLFLNSGSRIALHDWLNPAGE	SEQ ID NO: 60
JM 60	MLSGPNGRRQGPAHGIPIGPTDPRSFPRVSCLCRTAAIFSQPVVIFK WELRARGLLPRALSATVNHAVLFYRVYQSTRKDTPVICHV	SEQ ID NO: 61
JM 61	MFPSSFLNNENPETGRRFVKGVQLALDLCDNTPGQFKLVETPLNSFL LVSNVLPESRPVRDCPQAEGFDFEHIHLPKLTRMQRVLGRYCDHVNN DDDMCVNVKARSSNAQGALFYLPYGQDEWNWALTLRKDKLVKMAVEG LSDPTTWKGLEPVDPLPLIWLLFYGPRSFCREPECLYERNFGMKGPI LLPPHMYAPRKDVMTFVHHVIKYVKFLYVNAGGGLETELSPPFEASR LRSAIARLGDVEADDAYLSAKCMLCHLYKQNDTISIHETHVGGVIAL GGDGARYITSSVRTQRCTSRGDFVLIPLYNIEGLVSMIREHGLSNS	SEQ ID NO: 62
JM 62	MWSFGDSSSTGTDSSLSVPRISSSPYSSSLRSRTASVTASNSSIFFL LNPFSNPNSLCFSRSDVSSVPTTVARLSFFFRLSYDRSDSLVPLYCA LNTALSAPNLSKTEMDSFLLISDSSSDLINNFLAVAEAMFPYHAYEP FNVVQRD	SEQ ID NO: 63
JM 63	MASATAKKLLIKSELESEINKKLSISVFDRFGADSAVFNAQYKGTRE SLRSYDSLKKKDNLATVVGTLETSLREKQSELGLLKGFNRKKIEEFD AVTDAVRDLKDELYGELEILGTLNDESVPVEEESPKDHIIRWKLERL PRVCPKSP	SEQ ID NO: 64
JM 64	MNLFPWKKSPQRTTLLDGNWSVCQECAPKALDPIPKVQTDLDRTALS HITVIRTRKTLAQLKIPNTWSQCSHQATDWTAVLGRGSYGVVRSMSL GRCVKHFGSRREFFYECIFNDIVRARREKHPLNRGGDRILCFLEPCV PCRALIFPQLTGNLLNADFKHVNPERLAVEFSELREGVSFLNNICGI VHCDISPENILIKGELTTAYWRLMIGDLGSASLHTGTPWTGVMVTSK LGFVQHTYHFKAPARFICKHMYRPSCLLYRCLLSCAGGPQARMLDQP FQITPQLGLTIDMSSLGYSLLACLEKYLQPADPFPQQGALADASSES AHPLFYLRCMVPRVVIAEIFSVAWDVPLDLGIDSSGHAPAIPLREAY RRFFANQCSLYRAQYKEDALENASSRLCNSKLKLVLQKLLVRDYFSH CGNCGDHGFFLR	SEQ ID NO: 65
JM 65	MDFFSDEPMVQEMALLDIDEQQRHLSKMSLANFLKHERVRAFFNDNK KKISMPAIRFVYNFYLFAKVGDFIGNTEVYDFYVSCVFRGRRLTLLS DVYDACLNMHPHDRHHVCALIEQVTRGQNINPLWDALRDGIISSSKF HWAIKQQNSSKKIFNPWPIVNNHFIAGPLAFGLRCEDVVKKILATLL HPGEAHCENYGFMQSPHNGVFGVSLDFGINVKSNPKDGLEFHPDCKI YEIKCRFKYTFSKMECDPIYAAYAKLYQKPSMQTLKGFLYSISKPAI EFVGEDKLPSEADYLVAYDKEWEVCPRKKRRLTAVHHLVKKCMIHNS TAPSDVYILSDPQETGGQINIKAHLSANLFINVRHPYYYQVLLQSLV VQEYISLSKGTKNLGTQKNFIATGFFRKRQFQDPSNCTIGEFAPLDP HVEIPTLLIVTPVYFPSVAKHQLVKQATEFWAASASEAFPELPWDLS SLCANAPPTP	SEQ ID NO: 66
JM 66	MKISRSDSFILSSWVKLLVILGLMFIMSAVVPLTATFPGLGFPCYFN TLVNYSALNLTVRSSAKHLTPTLFLEAPEMFVYISWAFLVDGYLLCY YAWAILAIFKAKRVHATTMTSLQTWIVLIGSHSVVFMSILRLWTIQL FIHVLSYKHILLASFVYCIHFCLSFTHVQAMISCNSATWSLRVLEQQ IPENSLLDTLLRYGKPIGANLYLSLIAMEMLVFSLGTMMAIGNSFYM LVSDIVFGSINLFFVLTVAWYINTELFLVKYLKHQIGFYVGVFVSYL ILLLPVVRYDKVFISASLHKVIAVNISMIPITCILAIILRIIRNDWK WCAKAPEYAPLPQGSKEKTTKVKYSPELNALYETEEDVSDDEDAYPK YI	SEQ ID NO: 67
JM 67	MYTVYKRGQKYMFVRQHVNKQLNGPQPQNRHKNYAVRTYEHDPGLEA GHCRRVHALGLEYGQDGPRVVTQQISVHQKRPRDVNKHFWCFQKQRR RQVFSRTSDR	SEQ ID NO: 68
JM 68	MNAREVALTGHVLHISLHSTHEREKLIIWQVHLLVCQQCGIQGDAAY LFVTETLSNTDWGNIPAINRHAPSMNEHGRNYMQWELRTRLRNPIIQ	SEQ ID NO: 69

	SLSRQPGAVNVRVSEPNMVIVSCERALHHSCSVRVTGAYLHCNTTMD FRLDSNVSPTREFWFSEMFSKCLVSNIEVYLKTTGGLYYRASSATQC RKRAKDGALGILDIFNCESREIQVAGQKYNLSIATATFHVLWVDEAC MWNGALAEFFRALHNKLFGDREGVAPTLTYVCPGATPEGTPFPPYFS AFPHLLLVFGRPRRLDVTAVQELPKAQIAVHWPPFKNSILGDQLLIP GISPKKPGTVPVRWPLWVQDVNLSLCETTESVARIVDPHSIVIIKIS TLLCQHLKCHRAFVKNELEYIATICSSDLRLFIQEEYNRLLATIFTW AAASGYTWAAIDKTTVFIKAPQLSAAVSGSCPSLNSCRRKQYYKGLK ITVHFLSQEQQKVVTRLEAQLGLPVQETSRPPDWLKYEVCSASVFLK IPAGVLYAGLAKDPVSEAKRDSWLDCLVEGATLSLNNSVPPIGALAG ILPTLFAKRRCVNFWLLPREWVKSAPICPPLPIDCVTPQQFVVTKRG PICWYKEWPLPVDVDFMYYLQEALCVFSVVSNGEGTESHADDIRQLE KFEKVLCLF	
JM 69	MNTVVLSMAAQVYPLAAAHVKIVASNRLYSSWMKRRRSLEQMVAMYS NSFLTNARWHFRCWHNSVEIFMITIECGSTMRATLSVVSQRLKLTSC TQSGQRTGTVPGFLGEMPGMRS	SEQ ID NO: 70
JM 70	MDQILKRLMGEQHRSEAIMPETECASRGPYNYPVLPRLMLEVHKKNS ICMASNTPKLCVRGRLNVPDLGVHVRTRLQSATFTGFVFACVVEHED MVNTLDIYPHVFSDRVQLFKPASASVTELCCILSMLENYDKPPLSFI LSALDRARYLHERYTCNDSAFILYGIEVIASTLAAYHELNPPQGVLR VPPLVRFKLHKLLDENADDMKGLLKPIYLESFRLTENVEEDSHGETF NIFYCGTIFTRHLHNASVLKYFQITSLHSLPRQTLF	SEQ ID NO: 71
JM 71	MGFSKPFMSSAFSSNSLWSLNRTRGGTRKTPWGGFNSWYAAKVDAIT SIPYNINAESLHVYLSCRYLARSSADRINDRGGLS	SEQ ID NO: 72
JM 72	MFKMNPGLGSTCLVHPTELSISLFEILQGKYAYVRGQTLHSSLRNPG IFGRQLFIHLYKTALGSCTYDNVLKDWTNFETTLKTRWRGVEHLTPE FKRSTFESWARTVRLTVDQLLLNTINQVLHTRTVLSYERYVDWVVAL GLVPIVRRAPDGETIARIQAHCQQMRKTHASGDVTISRIVDKLAQEI TAIMTDVTSIYIPDYAEVSVEFNGDKAAYLGTYRQKDITVEVVSRPI IYNGRVSFDSPLYRLFTAIMTCHRTAEHAKLCQLLNTAPLKALVGST CNDMYKDILARLEQSSQKTDPKRELLNLLIKLAENKTVSGITDVVED FVTDVSQNIVDKNKLFGTGTESTTQGLRKQVSNTVFKCLTNQINEQF DTISNLEKERDDYVKKIQCIETQLLQSLPEGGRPRHDINILTQNTLQ ALSGLRDPTINLSECHIPKGSSVVNSFFSQYVPPFMEMLRELTSLWE GEMFQTYNLTPVVDNQGQRTSIAYSQDTVSILLGPFTYIIAKLTHMD LINHSLISLSLHDIADQLYVDSRLFVYINDIGHKYCEQIIQPGTDGP NTEAFNGGAAPIGGNNA	SEQ ID NO: 73
JM 73	MESSVGWTKHVEPSPGFILNMTSDAKVRGVVDHVSRLSNITTSPPEM GWYDLAFDPAEDSGPFLPFTVYLITGTAGAGKSTSISALYQNLNCLI TGATTIAAQNLSRRLKTFCPTIFSAFGFKSRHINIAVRKAHQTGAVS IEQVQQQELSKYWPVIVDIMKEVMAKKPNGMYGTISNADFETLSRMT GPCLWTSNIIVIDEAGTLSSYILTTVVFFYWFLNSWLNTPLYRQGAV PCIVCVGSPTQTNAFQSTYNHGTQKTEISSCENILTFMIGKKVVSEY VNLERNWALFINNKRCTDLQFGHLLKILEYNLPIPDEVMSYVDRFVV PKSKIMDPLEYIGWTRLFLSHSEVKAYLTNLHTCLTLGGDTRDTKLF TCPVVCEVFVKPFEEYKRAVNLTHLTVTEWVTKNLFKLSNYSQFVDQ DMSIVATESTERSTQVTFITKFVKNSHVSLNGKTKKCICGFQGTYFE FKRILDSELFVETHSQDRPEYVYGFLNTLLYNAMYSFHAYGVTRAHE KYLEDLKFAPLPTALATGRVDFQTVREELNLEDDIFYHVCSPPPPAG ITSLQVLVDTYCALKDVFASRIKVACRWFGGEFEKETFSAFTVNMVV RDGVDFVSPSERLNGLLAFASTVESYKIKGYTFLPIAFGRCQGLPLS DDLRKKMPSLVVQDSSGFIACLENNISKLTETMDDGSVFQVCCAGDY GVSSNLAMTIVKAQGMSLERVAVVFGAHKNVQTSHVYVAISRAVNSN YLVMDSNPLKTLLREPVDNTSAKHIVRALHNPNTTLIY	SEQ ID NO: 74
JM 74	MVSVSLDMLFSRHAIKPLESCTTRDGIFFLRSSLSGNPWQRPNAIGK NVYPLILYDSTVDANANNPFRRSEGETKSTPSLTTMLTVNAENVSFS NSPPNQRHATFILEANTSFRAQYVSTKTWREVIPAGGGGLHTW	SEQ ID NO: 75
JM 75	MAMFLSDPPRTPPATPRMLPIPGAPRKKRTRRFLFAGSRTGLPVPPG YGGPPVIDMTAPNDVFDADSPPTTPKTPDETDSHSENSNYSDMDEED	SEQ ID NO: 76

	EQPVSSPPRIDPHARDGESFNQSDWRPTVITAAGPAAQPSAPAPLTA FGGQRPVAVVTGQHRAPPSSTSDSGDDFFIDDYEDTDESGEDADGFS PRASPAWSGDTSRSPAGGGWSSNEEEEPAVTGSAVEQETIIISDDDD TDDRGSVETWDESDADEGTGATDVIDLCSSSDSDDDADHVTSGGVRA ACKRHASRRDCNGDDDVIYLGTTRAPKRRMTSTTGGGATSNPEGPGV SGRQTMAATPPVCGNDNYPWPWLD	
JM 76	MRVGFVWRFWSGGRRICIKNIVRCSHVNHRGASVTGRYRQPRTGPGE QKPSCSLFPRCTGNRQHPGSGRRGPWRVRQEHSHDQNVHL	SEQ ID NO: 77
JM 77	MDTWLETVVWHKMSMTGPNETPTQMLLISDSWLKFLNLSPFLKKKLA ALLRRVMDMSKATVIYPPIDRIMWWSYCCEPEDIKVVILGQDPYHRG QATGLAFSVAPDYSIPPSLKNIFKEIANTVPGFTAPSHGCLDCWAKR GVLLLNTILTVERGKAGSHSNLGWDWFTSYIISCLSAKLQRCVFMLW GRKAIDKAVLINGQRHLVLKARHPSPLAAAHAATGSPWPQFLGCNHF KLANDYLVQNQRGAVDWNIN	SEQ ID NO: 78
JM 78	MYTLSFFTTYFILYIGYSSGLIPNPCCDIVPLTGVNIPAPFEIVSFH FTDLAWCQGRCVATLRYKVGTITTELCVNGFHLRAFFIRILSGLDFS VHREELDLLNYVRISLEDFLSAFKDTHDNSESVTNLPAVPDLTKKGS AAFRTRKVGARRGDLWILGSRQ	SEQ ID NO: 79
JM 79	MAVSIPVQGVDRETESNWRSIVTTFEQHGNADRAIRSLLRFFKGVDH PGFLASLVILKDVAIDSEKTIERTDIIPLLQGVRFVTQQIYMHLKDH ASESPVTEIWRDCKERFCLALELACGCQSCTSAARQLRDCQQACRPP KLNPHKQQCGAARLLTAVYNQMVLRTRVSVSEFCLNALMCVPREFGF VSGDVRVETSRVASCMNLSWLYLILDSYIRTDLTNLEMAMSRACRIR GLSTRDPFYSALVWLKNSCACAANTFFFTVNSTRVTTPILMDICASL AGPVPDVIKINMLPLVNNQMYPSVCVERANFTGSCPKMSPTHRFDGL KLETTSLTLAADSLDDILQALELICDDDEGILDSHISDIDTETEVDE STIEEEIVFEELS	SEQ ID NO: 80
JM 80	MVDPFKKSQKRPDGSIRVSMLFKGSHDGSPVRLGLPVNTLNWNGNSH DTVNFLMSPKTNPETELNTNDCHPYPKPRPRTIRPG	SEQ ID NO: 81
JM 81	MDTDDNQVIKLFFIQDSGGRVYSGVGGSISRRWEWLMNPHLVLGSGA LCILLVQLNLNLACLGRTNQKTAWPRLLGALCKL	SEQ ID NO: 82
JM 82	MSRHYGKDHLLNHMYKFHYPPLGMIVGEMNTLTVNARNPLYQAATLR VERALYLSKILQVLMQHRQGERFIVPQCRSNMVYCLKELHKITNDRI RGLINSVLPLVDAGCVGFDEELVRILPEILKLEYPHVHELLPPHDPT SPLSWCLSHMVGVTKTFKGEVKEMIDTFHDLSVPSFQYLASLVKKFF LVEEVIYEDYQDTQFNVFLNLCFFWTTVIKMYQSCIFKDKLLDTIKA CIELLKGEARQFFGWYDLNTPNLGSAALVKYTEHLIRALSVDSSAIP IGEICSHLHHCKHALLNLE	SEQ ID NO: 83
JM 83	MGMADESTLSARIRCSVYFTSAAEPKFGVFRSYQPKNCLASPFRSSM QALMVSNSLSLKMQLWYIFMTVVQKKQRFKNTLNCVSW	SEQ ID NO: 84
JM 84	MECASLGPISGLIADLNLFNLFCLYRGSRVKTRGAATCNVPCAECAQ GVVRILTERALCCTEKMFIASACSGVVLPPQLAKVFHDVYAEMKAKC LGAWRRLICCRRPIMAIADSVLVTYNTLDAEGKLDLKLKALCKLVFQ PIFLQRILAPMQLLANGKMVPDNYFTITGTAEKRRPVVTGSTSGMTC PGSSLVPDSLILPVCEPGLLPAPLVDLSNVLENPEIILSAPPLSQFV ITNTHPSLPQSVSIITPTQGVVPGQCFMDTWKAVSQSIHHQAHTPIF AATLAGSTSAAPGPHIACSPVAGTSRQVEASAGVDCGKPVCAPQPDI PPHVPTKRMETVAQSGNAPVKNVHIGGRVYAPLVNIPIIDLTSPSGS GQSPVNIANTPESRMAAGSPPFAETAATVPAKRKQPREDVADKRSKG DGRGAATVNPPFPGPPAMRVREQGLFDLIESSTDVTANASGPKNDDD MLAAILQDLYGLQSPPAIDSPSSNSDNEDIFPEVSPPSSGHGSP	SEQ ID NO: 85
JM 85	MSSLSELLEGESIAGGDCRPYRSCRIAANMSSSFFGPDAFAVTSVEL SIKSNKPCSRTRIAGGPGNGGFTVAAPRPSPFDLLSATSSRGCFLLA GTVAAVSAKGGEPAAMRDSGVLAILTGLCPEPDGDVKSIIGILTSGA YTRPPMWTFFTGAFPDCATVSILLVGTWGGISGCGAHTGFPQSTPAD ASTCRDVPATGEHAICGPGAADVEPASVAAKIGVCA	SEQ ID NO: 86
JM 86	MPRVKTQPKRPQVFDFMPLDLHGETRAEMDSQSLCPDGQDLLGSYIY TENNGPFSQMMHNGQSNNGTGESFGSYAAGDGFLGGSVSGMHGNGTV DGLCSKKQSACRKRSAALIHAASEASVAEQGTSQGTNAVSDRIGRDG	SEQ ID NO: 87

	GIGNKLLKVSARLPDKTKTLPDPSLHCYF	
JM 87	MRIYGIKGLNFFGIMGFWNIPLGWGLCFMVWVAWIARGRSVCPTWHL TDGKYEAVYRHYLEECRKHEGSGSPDGSGKTEGSGTKATTEANISIR PNVVTSGQDKEPMKTAPRAESSHDLPRIEQVNALHLSTPELAQPLPV VESTPRESQSGGTPWDARPHAFIMHTNDMLNPSVVLSFRAVRARSIR DTEQSIRDRNTVTTSYRTPGRPSLVQARPSSYGARLPPSPRTMARYA ETRPTDDQN	SEQ ID NO: 88
JM 88	MDCSVSRMERARTALKDRTTDGLSMSFVCIMNAWGRASQGVPPDCDS RGVDSTTGRGCANSGVDKWRALTCSMRGRSCDDSALGAVFIGSLS	SEQ ID NO: 89
JM 89	MSSTRPKTRAPKKELTMEELAAQVQKLSVENKQLKKLINSGDPTRSG SDPVISNSEKEAKIAAAVSALCNVATRKIEAKVRAVTAKAVTRGQVE EALAGINIRVDVSMDETTRGGITASADGALRRRRAQSRTRNNDAD	SEQ ID NO: 90
JM 90	MTGSIVLALALTACLYLCLPVCATVTTSSTTGTGTPPVTTTPSAAPS VTPSFYDYDCSADTYQPVLSSFSSIWAVINSVLVAVATFLYLTYMCF FKFVETVAHE	SEQ ID NO: 91
JM 91	MAEVTAHTVAYAFDSCKFEIIPKNNSSRIALRNKFPVVVKPGEPLVV PLGLRIIRAPQCAFFLSGAPTDEVYYHTGLIDQGYRGEIKLIVLNKT KQSVTLYRGEVNVSLIAFMYASPGPLKCPILNLPHYSLDAGFDVTSP HAMTIPPTDRTPFTLSLYYKSPQLSTPHVPLIVGRSGLAAKGLTVDA TKWTQSLVHLRFYNFTKEPIDIPANSRICQVVFIHEDHVPSGWNILR SRVQLGSTLQISWAKIRFTDVATLPATHPLNSRPTQSQTEPETNRGA KGLGSSGL	SEQ ID NO: 92
JM 92	MSGSVYSRRPRPKRVEHSEIPRTTRQHPPDIVGQNQVHRRGHASRNP PAQLPPHSKPDRTRDQPRRKGVGVVRVIILKHGIILKLFIFNKTIQI NINHQPGHLVLFCLARYYPPPPTGASVVESPDGRGWRTLRYLPAHY	SEQ ID NO: 93
JM 93	MAAPGSFWTCCGFSPFGRVGCRYRPLPDPLNECPTHWRTEIAMGLPP GVDMGDVKQAEMCTAALRQTYLLAVQSNKITEYLRRFDAARVPAGCQ ETVRIQISKLKSIQNVIWNAMLSLAIGDITVDESAFHALLNKRADET VSLLEMEKLATTIASDDSVTWAAEINNVLVDTEASSNPSHPVIRQPT PQLAVADNIVPDKIIQDAQADG	SEQ ID NO: 94
JM 94	MSQVRPLPDERVNEIRAIFSTSGDMAEVITDILTGTQATASFFCVLH DRGNVPINTPHAVIKLCLPARRPGGGPRCLPLMVLNLPAWQVHLFLT GDAPLTSDNIKDRIDLAQTEEILEPILSVLACKRSAQQTKHDSFKSK VAWFRAKFVSALRKVYKMTPSPYWMITLLGSFEASFVLAGTFYFFQS YTCTAETLVHLTRLFISSQGQSLVTVNTYDELGRVFGRSDFLEIVPN FWAYLKYKMQQDDVESKAIDQTINSIRGGLMLSPQDLVHFIYLSFYE CMNAQTFLSYSRTTASLPTPATVNPPQLCRRLEADFKEHVMAYYNKA SYLSTYITILTVPAPLPEGYENFQELACQYWCGQSRDVAEIMTRIND QYPQLNLTKDLSGLLDLAALDQDSGGPKENLFTVASRIPTYRCEFLN KQYFVLMHTDCIDAYWKQNIIVPEDAQLQGLTDQDLTSRIFYCDLGL SLPTFKQQIMVSRHEYFNPRLPVYRWVLDFDLKVTEGRRTLNDIYNI CVTLRQVILETLQLIGPLKPHHPVYFFKSACPAVTWPDDISDTAFCH CDTKIGMRIVTPFPIGYCLVGSAPLVSLTNILNRVVKLDTRLASEYP GILEDKGPFDSGIYAKGRCVRVPHCYKVGPGGELSRLLKIIICHPEE SDKSAYLKNAFKVSNLLHHAPGDSVTKNGHLVYAIADENEGFLESKT KNNLPKTITDLAEKIERTTEKPLIDWAATAVWPKLHDTIQRFFPDDR IGQFASVSFMHSGDNIIQVRPQKGNNFFCINHKHRNHTQTVRVFLTL HSTKESEVTVTFMSQCFAAKCNHNSPTAHFSFMVPITCT	SEQ ID NO: 95
JM 95	MLSPECMKLTDANWPMRSSGKKRCMVSCSFGHTAVAAQSISGFSVVR SIFSAKSVIVFGRLFLVLLSRKPSFSSAIAYTRWPFLVTESPGA	SEQ ID NO: 96
JM 96	MAQAMVSLEYMKDILDGKKTSYGSYNFYLKPQLTKRLVLYALHAVRV SRTNLFYRGHIIIGLRRLLIGRDGRPVPDAGARTVHGTAQLS	SEQ ID NO: 97
JM 97	MRYVFHALICFIGGISSSDFDDSSSDEMDDLSPTPEPEPSTAPHSFP EGPKSKVVALPKIRKRSRSKTPVKIEHRSPLNRSRSRSRTRSGSGQR TSSTYVKRFKPTVDAPRSREPWHRGGKGKAPFIRRNALAERGRRTYG NEHRGKSALTRNIKESIKKMHLPSTMLSRPHDKKVFEGLLPRHLEQC FQVCLPAPPPLRPEVFTDRQLTAIVKSGGRRDALVAKKVSLAKVMSM YKPLLTFVTGRNNQAHWLATRKNTLASAGLEALAAFIEEGLAWAQVC VSQNRSLNDSNLDIILDSSQSVCTWFISKIRHLHIQCFLENQGEISL	SEQ ID NO: 98

	VKQLTYLVCINNRLAEAANLAGEVKLNFKFAMLIGFALTLPALLAEQ KLSGESLYLFRSFLEKYRPGDVMGLLNSIVVEHYTKCRSAECVITTR AMVGSGENNKGLFFFPA	
JM 98	MATWCPPHSGGPSAMGLREWIVTHANLGTYSGLFWADDEKTRVVLAT TTAWTVEFDYPRDGKVYEDYCNQRNIPLPSGRPRLCQAKARLLGAIR KSAYFVEEKNFLRRSFSFPTVVFRLRSNEEMSCRLCPRASGVAAELR GLRFRMFKRKGADDVGRVTEYTVKQLLGLLRTRHAGASTMTAPATEA SATTAGEDGRQDESEGGAVALPEEHTPPLSVSSGLSACLAPSVDDPW GFMHIQVYYYGFLQSQVFTRTGMGVRLSTRPTDKNEHHVCMAHGPLQ LWLPPAPHMDDDVMLSRLVNALNALEDGIVLSSCQYGIMMNGYGFLN LWFRGNTLNTLEPTRVPSGVGHRIFDTDDYITKLAQSPRPSDPGPPD PFAQIWVAAWSLYEEEDLSQAPICIIVHQREIYRHFE	SEQ ID NO: 99
JM 99	MAPNTQKDRLIQIAAECVPRVTQPRPLHSRPAYRLHRRWLRTPRWPG RSWWRHRRDGYEAARAAALPCIQLPCPHRRRPCA	SEQ ID NO: 100
JM 100	MRLPVGADVCSRHEIIPPAATNSLSAQSAGYRLISLTSTPPHHLHRS CPCPDCPLNLVRSRPALLPGQAIDSSPLRDLPYGRNRRHEPLMFQLS RGKNNPRCRTQTRFRTRNAVLWRWVHGRDSATEPTDTGRFVHNL	SEQ ID NO: 101
JM 101	MAGRGVDIKAWLVAAVESSEYHGLVWENEDKTVVRVPWNKVTAARSD SEKFFDDYCNMRGICQGEKPPHYGRFRKMRFLYDMRHHKSIRELKFI NKAYGRSEARYRLFRLLPEPVVSCAMCNLMSSTETQCLGLTSEFRYD QWGGFGRERRRVFTATVLARSWMDKNKRVREHRLPGAIQLTFLYFGS TVGLERVHAGTRVCSRPYPVLAGHACCFQDERTLFLPPPGVVDCSFA REDLRGMHKKCEKGLLIALTDTGISVKNLENREMKVLTNNEEEYKDL PSRQPVQVFDMVDYLRALARSPKPGDDPPRDYAQIALCLSVQSPNPA HAPIAIRLRYVCETSSVCGTEGCFYPGTIGTSEARVAGSFHMEDPGE GTSQSLDPAVELGDSGPDSMDNPDTGTSGEDDGVACS	SEQ ID NO: 102
JM 102	MGGIRRLNRQTQGDLCIISRWVVSRLRGPCKSSKIIHHIKHLNGLPG RQVLILLLIVSKHFHFPVLQVLYGNASIRKGNQQTLLALFVHAP	SEQ ID NO: 103
JM 103	MERPVRVTKPSSLRGWLVECCETGRHPGMRWIDDERTLIRIPWNHDR GSRGVEESEKNIFIDYCRSRGILHAAGRELTAKECKNWLSSAIRHSQ TVSDVSTNDDLSTPYPNRCRTIRLLPITVRSCARCDQASGTTAMLRG LREEAVNKFGPVGAGVQYTGAVGAGGEQCWMLRITFYYYGDRFGEVV TESPNGIRVLPLSERRAQGHICVAPIAEQALVPEIPSHLVEFQAEAL RFLDKDLLRGLAFWADPSGIYIRWLGHSMAFVQGNVESPGAIVVLSC ANACRAFNLVDYMKGMARTPRDGTAPPQACVYLYFGGVPTPEGGVQS TVPLIIQLWHECLWQALSAANV	SEQ ID NO: 104
JM 104	MAIRDSNYSHLRSWTLYHLNEKTYSDLTWCDQEKKTFKLSWKKGAAG TPAVVAYCAQRGLQVGIDGNVFECKRRFLRGLRENAGFQECEHGVVR THGGGWTAFRVKPLMDSGCFACILDENSEGIINYLEQVCGIGLEPGM PLPAPLPTLVPPTRSAYARAHRLGVPEAPLPHQIVPFWRLRIQVFYF GVLALDHTSQDRRGVRLHPRPVPRPGHLCFYGTGFTVWFPSPDPGKL TPDQITQINTMLVTYNEGIYVHGNETGVYVDNRNRETLYAAGNDCNG DIIQREVMFLSKQQIFYFMGFMRKLARSPVPESHAPCNGATLYLSQQ PGAQESPQVPISVVVCQDELVQGQMNPSRWCA	SEQ ID NO: 105
JM 105	MALWYRGAGKLSHETHEIKNLLFREEHDLSLNNITITVVTRSVKRFP VPIIDVHSGFIAVYVDALVIRDQHCVYLRYLIWSQFSRIWRWKPNGK PGAVKTQMTGTWNRARMQTNTSSILGRMIQCQNAKIKHLNS	SEQ ID NO: 106
JM 106	MAAGESRRGPSRYGMALREWLISKADSGFYPGLFWADEHKTRLVLAA TSPSLPNYDYQRDGQHYDAYCDLRHIPLPSGRGRLCQAKGRLLGAIR KSKYFDEDKDFPTDQFPFTAVVFRLRSFEEMSCPVCPRVDALRLELR NMRFAMLGRGMLHAFPESSVGDHEARHLEGQEGGDDARDDDAPYSSG VLRARLMACAAPSAGDPWGHMHIKIYYYGQLQAELSTATGQGIRLSS RPTNKSGHHVCVLDGPLQAWFPPIPQITDTSMGQRLEDALKWLVDGI IFCSTSRGIVFTITGAPNVWFQGNTVEPRNFPHRAYTGMHVWAFDTD RYLLDIARSPSPHDTDPPAAFVKLWVSGCSLGEERNVSRAPLSMTVH QTEIYRHFE	SEQ ID NO: 107
JM 107	MTQLRPYCDKHRESGTRVLLWPFCQMNPTGNIYFLQYGAKVETEVLP VVPEAPPRTPDGPSSPLLLPVALSPVSTDTSSHT	SEQ ID NO: 108

JM 108	MAEQNMDLKAWFIDAVESRRYPGVVWDDDDRTIIRIPWNRSTDSRID EEYNKIFDDFCLARGVCQSGSTAHANKFKKIRMLYAVRSHRYLRELT PPSKAGGVSGERYRLFQLLPEVTNGCDLCNLIATTSLHSCSMGSGVR DDFFEQARRPRARLPLRVSIQRRKARLQGSPAQAAPGAIEVSFFYFG ENVGVEILRSGCGVRICGLPDPKRPGHLCCADNPLTRFLPSAQLVPC EFARADLQALQKTCERGLICVMVESGICVKNLEERNMTALTNYSENY YELQPTQQFQVFDLLHYLRALARSPTPGDLPPRDCAWIFLCPSTQSE NTWDAPIALKLRYVCDDVSVETGDSATGSNSGDEGPSGVRGGASGTT GSTSVSTFAPYWRK	SEQ ID NO: 109
JM 109	MLRSSRFFTQIPDSTITQIRPLSHVFCRACKSALANSHGTNCADGRK RVNGLSAQHRCPGRLGSGRPHIRTPQPERKISTPTFSPK	SEQ ID NO: 110
JM 110	MRLSVDLFHGIRIMVLSSSSHTTPGYRRDSTASMNQAFKSMFCSAIS RVHHLYRAGQLKYRAHRTTSLRDQKNLDLKEAYLYTPTGQLSNK	SEQ ID NO: 111
JM 111	MAEGRAGSIRVNRPSGLRAWLLDCCDNGKHPGMHWLNEEKTLVRLPW NHLKGAGGVSENEKNIFLDYCQFKGIRHTGNRPLSLRECKNWLASAI RHSQTVEDVSTEENLSAPAPYRCRVIRLLPIFVRSCPLCNEADATGG MLLDLRNEVTARFLYLGAGREYEGAVGSDGVRCWMIRLVIYYYGRLV GNMEVGSPNGVRLLPAPKQPLQGHVCAGIKPEQVMLPHNPHNLLPYQ TSMLRWLAKEIIRGLMIYADGSGIYVRYMGHVPAFLLGNGGSPEPVD MINSGRVARVFSLVQYLSAVSATPPHGTLFPAAYASLHIGGVPTPEG EPCPTIPLSIQMWHECLWRACGDAAM	SEQ ID NO: 112
JM 112	MAESEITHNHLRRWIISNLEANTYPDHLRWCDEEKRSFKLSWHRGMQ GMQPVVAYCLDRDLQCGRQHNVSDCRKRLLRVLRENAGFEQDDTRAT TTNSGGERFFYLKPAVDPLCYACILDSHSETVINYLEAACVHGLEPW TPLPPQAPAEASGAARSVYARAARLAIAAPPHPEQITPFWRLRIQVF YFGSLVAEHTGVDRRGVRLHKRQDPKAGHACYYGTAFKMWLPTPHEN GPLTPEQRETVCEIINYCEEGIFLHGNELGIYVDNRTRHTLSCAGND AEGNHAQRFVRSCAKFQIFYVMGLLRKLALSPVPGDPVPINAVTLYL GGRPGSRKRPQVPVILVICQDELTHGDIRPARWIL	SEQ ID NO: 113
JM 113	MAMSWGYMWITEQGTLFPAPGTTQRETTHSVLCDPVPNFRFFMLWVY CANSPFPPFPATRFPSTQSLFTLGVALAPVKDPRSLSFW	SEQ ID NO: 114
JM 114	MDLSLGRPYRLKLRRRLVVRRGPFMPEPPGWQLPRHHTRSRSLHFGG YVYKFFILDRWWRNTRAWIVEGYACISAKTQKLAMRVIMGQRLRCGF QRRMRMDH	SEQ ID NO: 115
JM 115	MGTYTSEASLAWLSFMSGTVAASPFILCFIYHSLYFLEPLNSVENII FSWGAVGLHGLLLLVCVVGPPAWLSRQVDVPCTISAILITAGSMAST LGVDLPWVYVSFFVGSCLCLLLCVVVANDVVYLCPTIAHRYYELGFF AAFSVYYFLVLKNLFLAPVFLLPLVAFIVGGVCSLRALRSHPLYEAG LQRRHAIFSLTSRRYITYSIKQALEVCGWDFYLVTVLIGGAAAGTLS VGLTTPLLLGLVHYFFVFHVGLFCCIGLVFRSNVLALVYVLAAAVLL TLTHVLGPGTHNLFTRVCVFTVFLLTMFGAIGCELQIIRKKLQRAAN SPRIVLGVCACGNLLMAVVFFSLNKVELVAL	SEQ ID NO: 116
JM 116	MPVSFHYGARVDVDALGNISKVYDHIKGIVKKGVIQISGQGRAPVLS VLSSVGDAGVLGLRLKNALAPLMVYSDMTDEVSFSFRNTSLGNTFTH TREMFGVNITEMNVAFYHHGDESNAEGKPQFVRTTIAYGDNHTSTVH KSVVDEPNLPSFHDRLEQAGTGNRLFLTVKTLTLLSKWLRQQKTRAK QVVTVSLSETLAVATFTVDGVSKIIDFKPDTPDAKWTCAKGRKLDVG VVSSDLTTHVSLESLVAALNACKIPGFFLPGFRWHANEILEVEGLPL TDSLADVKLGVMLLKVDPTDRNNAVPGNLSEGADPEGVPELPSPPRT PDLDLKEQCVPNAEDGTEPTDGGAKSLRTSGSRPEKKHGKRKHSSSP SRGKAKTKTPRATFNPLF	SEQ ID NO: 117
JM 117	MLTPNISRVWVNVFPREVFRKLKLTSSVMSEYTISGASAFLSRRPRT PASPTLESTLRTGALPWPLICITPFLTMPLMWS	SEQ ID NO: 118
JM 118	MSGLSIVTAAMESPDRFLYASDHPGFLALTQETWQNRWFPSQISLHE DSDEVRLLSPTDREFYQFLFTFLGMAESLVNFNIEDLVKEFSNHDVT HYYAEQVAMENIHGKVYANILNLFFGGNRGDLMTYAKKIVEDATLAK KIDWLHSRVRKATTRAEKVLLFLVIEGIYFISSFYSIGLFRLRGVMR GVCLANDYISRDELLHTRAAGLLYNTMISRDESPSVAYIHGLFREAV EIETLFIRSKSRGVTMVNVGDIEQFLQATADRILKSINVPPLFGARP	SEQ ID NO: 119

	PNACPLSYTSAKSVNFFERDNSEYVTSVHNDL	
JM 119	MNTETSFSAAKSAKPLTLVTNAETGGCSSSLDPERCAESLVNSLKAT LGWDVEANSLTGLLWHRIMEDRCLVTVKDYLTVFGEKLSDEVREFML KHEAALDGLLQDFKQSKAYANLVNCGYLSAVRFYDTYVLRTHGSSPI FESVAQMFMRVAVFVACQCIKFPCLRKTLRHLVQSETELDEMYLVGY AFHYISSQIVCCATPVLRSAGLRGGQLSSCFILKPSMATENKTLKAL HEEMSPLLASKSGVGIDVSSFAEHKNITSCLKLINAHVGYFNDNNIR PVGASAYMELWHHQICDFLNAKMPENQERCHNLFQGVCVPELFFRLY ETNPDGQWHLFAPEVAPNLLKLYGAEFEIEYNRLVAAGKHSSSLPLK SMMYALINTVIKTGSPYVLLKEALNKHHWCETQGSAINCSNLCAEIV QQPEGQASVCNLANISLPKCLRPPRGKSGVEPGKGDVTFGFELLDDA VEAAVIIVNACILGGTAPTESVRRGQKERSMGIGVQGLADVFAELGF GYLDAESAKLDVEIFQAMYFAAVHTSHEIVLLGEGTPFHGWERSRLA QGVFHWQTWDGVKPSHPPLERWEQLGRSIAQHGIFNSQFLALMPTAG TSQLTGYTEAFYPFFANIASKVTSKEEILKPNVTFFKRVKPGDLRTV RRYGGDVASFPEPLKDRYKIFLTAFDYCPIKQLERAGARAPFVDQSQ SLNFFLKEEQATRASYIRDLLLTGYRLGLKTMLYYCRIQKQTKLNAL QCLDQVVGDNTSSEGAESNRVQKADGEQAEVCLACQ	SEQ ID NO: 120
JM 120	MTPWRPQLLLSMRAFWAGRRLPRALGAARRNDQWALASKDWPTCLPN SALATLTPRAPSWTWRFFRQCILRRCTRVTRLFYLARGLRFMDGSGV DWLRVCFTGKRGTALSRPTRPWKDGSSWGAASPSMEFSTASFWR	SEQ ID NO: 121
JM 121	MERVTNQVHLVQLRFTLHQVSEGLPQTRKFYALTGHKNSHPHKHLGN ALKNGRRAMGSQHVRIVKPDGRQVAAVNEICVCLALLKVLQKTVKGR FVF	SEQ ID NO: 122
JM 122	MKTRDANVNKLNDSLMRLLPPPHRVSLSRGRDFSKGVRDLLSKYVV STTTGVEAIKDGFLSVSPKCQTYGDFLIYSQTMSSQEPRGTYLFSFK QTDTGSSIDMLFTPTSLARLSRMDADSAPQTNRIACVWYGHESGLLD AIPNFEELLETGSLHQFLAPVGPLVQTVHSTFVTKVTSALKGDVVAR EPVVTHIGLTLPSDMFVDLDDSCPSSLRDEPLPAHSSIYVCLTYIRA NNRPALGLGFFKSGKGYCEIAAQLRDFYSGVIRTKYIQLQNDLYINR LAFGVVCRLGSVPSGSQPSFQSLHFKGAALPVLKFTEFVSNPGSWKL FL	SEQ ID NO: 123
JM 123	MTSSISAARADNGDENTGGLYRLIDNLLTCTGSLQQLKLLMEFQLKP LPTAHLLSMPTVTRFLNTAFKIDNPLVSFIQKHPVFFLMRVARLPDP VITDHQSAETSTGILSEVVNVLNIAIQKPHESPAAKDDDYLDNRAIL TMITEYIHHVTSRTPSGIPPTPPMGISHLPCVEQILHETHRQYWNLA LPESLFIDTGEVASPLQTWLIISYCKKLQLAPPPLFPPADELARRLV TGHHELFVPLSTSLETYITMPVSKRRAFEIYSVFAKSKNIVDGTPIL AFTDTELTTFTPELLFLYDFVIESLCKNQAYGCSRNAIEHFIKKGID FMAELGAFIEKTCGYRSTVSLSNVRSVKARLASCGLSKEACEDFRTM ILMTPHETTPKWENFTDFLEMVNQLTLYGFYFYECLNQYSPTSISLA KIQNILNRVDAEQSDRALWRTPLIGSFPFPWKLNNVLAFFKPSAPVA TLQKIYKAIPSYLMRSLFEIAANKSWGNIALAERAPLTDIQTAEPDQ GPVPTQVIAKYCSRLQISATDYDAVIVSSPGFATEFIRTKLYPILSE VLRNTSKKNRSLFQLRWLIVFAAEDAKDLAPIRRSLALAYFQIMDIL EEKHSPESFYNLLDYLQDTFRCIRQVIPEATCPQEFLQYLFTFQNLP IAASFIQTSMTFVDDLNNGIPGILDLVSLGAAFYNMKLLYDSTLDTV EIPTEEGQPIVVSMFVFKSTIRILEKLLQEAVIALAQTSEPMYAAHI RLMQHLTYMQKIAGHEIMTTQLPSVFHEIHEGYLQCFKRFKRLMLHV TGSCCYSLTRYFGFLYQPPLIPDTIVQKILNFNDKTDTTDDILKSLS QPVGQEPLSAENESSSRLSKNDVELLQKLYDDFRNGSTNDNPTSIKL EYSGNYNETQVSVDWSTYNLVTYTAPDDTLKFTPVNTEALDRMLAE	SEQ ID NO: 124
JM 124	MELPPIFSKFKIEGVATTHQADCRFGQYAGSQCLSNCVIYLAQSYFN RESPVTDTNDLDDVLRQGATLDFILRRSGTLGYNQYAQLHHIPSFIK TNEWSAAIFQSQEYFGLIGLDAAIREPFIESLKSILTRNYAGTVQYF LFICGDKAGAVIIKNKTFYLFDPHCVPHVPNSPAHVISSADPTAILE YVSPPDREYTGSFLYIMPSEYVNPEHYITNHYRTITFAKVHGPQIDI STGIEPCTIEDIPSPPRSPDVTSKSSNLARVPKTTTDTSSAKTTPAP LSGLLGVEPPTSYPDPAADDADTKLLTPAPARTAVDHPEFQTTPGAT	SEQ ID NO: 125

	LLLSELSASRGRKRKLSSLQRYSDSDEASSDDEGAPRRRAHDDAISA EVIWMDDDISPLYSPSATPSFDDVFDSPPMSPEFTYTNATEDTDGAF LEQIVRDAETPFSAFNDLISDHDFSSLDKKIEQLIKYEAPSQHLPNI SDKRNGRAVREAAALQAMDKIMINIILEHGLITDAQARGPSACKNVL QFFILWGEKLNIPISDAKQVLELDLQLIPLHTALSEGKFKQGAFKKH LTTKINRCLASMRATHANAHKKLASAFNIEGSQISSSETKISVRALK EQIANHLSPGFLAVYSADELKHLRDKIRDLKTGIEQRNREIQQEELF FGAVLTALDTFQPPPKPAYPMEIFPHRKTDVMLNHLASITTRLTDDA TEALNNYLETPPDQGTHITNIPNFSSIVANIISTIKILTYAENDMQL NVTPMATYRRQLLYLGGELATIFNLEWPYETVPPVQELPLVARAKAK MESVTKMEKNQQALDQILGDAETLLDTITATSGNENPVRAMSIPILE TYITNAGALIGTSRNPRFEKLKAAIHDLASSESFIIMLLNNTRLDNI SDNLAKIDGILTNNTRFLSTATVTKTLQTLGSSLIRECVEALDKRSP SSLTDARLLAVQTILGHASVPDHETLTRIVSGVASAQKESAGDDPDR WTRVTGHLNELKLAATQSNVDKATRRKLLMIITRDLKEAEVSQETVL ETRWQENVLKFQPSTSKEIEDFLQSAPSAKARKFAEKHLRTLIAQFD GHEQRPSEATAVPMDYTPTPIPTPQAVSTATAEKGKAAWNKIQQAFQ DFNFHLIDASDWQEMASEYSRHGSSLPGTVGPKLVRFMESISNTLDD ILTQKLASLLPNGPAFRPPAFDWIAPYQTRVNAFLKTIGLPMVRDLA DKIHHQCQTVSHAVQSADLQQATVGTSLERPAAEYCRILSDMQVAFN DHGIAVRSEAAAYTDAINSPANVATPPKPNLEAPKKLMTATDVLTVE DFPEFLKTSILQQEQRLIALQRAEFQQLEASISAAERLRQSTRNEIA GKMATAITQLLPRAPVAISSRPLNLSKPIDFLSSTVYDKILDKEPYE TAIAGFAWLETATKSVMVYSHQNQTQQLNVLLSEVEKQSTIAQRLHD LEVSARNTDDVKVLKQALDELAPLRVKGGKTTVDAWKQKLESIESLL RATRTAGEISSELERIGAQAVGTIAVRDLGTLSDQCREAANFLKQAS LPEGFSDIGTKLSELQAYIKYKKQFLEHFETTQPNVFRRFPLSQNIT ENVPARLAMDSMARLANHLHVRGSAPHFTTWIETLPTVDPEKPTHVP AHGGAPLHRQITYSNVLEALFSLCSTTLTPVPTAPGLEIATRARRGA EAATWMDRQWPDIAQTLQDVLDTYEHTTTHANRDATSNAFLAMCVFT QIIRGASRAVTLPKLPGTAVDFPEEIVLTPRECTTLVTAMWPTLAAA ILRLKSYSEALGLMSRFLPLMFQALPHLTLEAQVQNGPHNTPPQVRC FARTEAIPYFPAQWQSANLEQSLWGQTDFLQICDNNQRKARVAAVTW ALTTINGVVLDQLWSTFKPMTAASDDTYVDLVKTLHLTTFGPRGPTP RRETTTEHPPYEYGQPTGYCISGQSTTPVQASNTPGVRF	
JM 125	MESPTVNIEEIYRRPSRSPRRISHRRVRAYVGPLRRQTTLRRNPNIA EGWTACVSDPWMPTVLKEVAWLPVLFGIRGGRRRFALERELRVLCPR RRLPGLGSLSVVRRPVDRIAVPVWFWR	SEQ ID NO: 126
JM 126	MILIIILSIAWRAAASRTARPFRLSEMFGRCCEGASYLINCSIFLSR EEKSWSDIRSLNAENGVSASRTICSRNAPSVSSVAFVYVNSGLIGGL SNTSSNDGVADGEYRGDISSSIQITSADIASSCARLRGAPSSSDDAS SESEYR	SEQ ID NO: 127
JM 127	MVWTARRRASVREDGLLLSSASTHSRIRLLPSVWSVFVTVAVERKRV LLVRMPSILARLSDMLSSRVLFSSIIMNDSDDARSWMAALSFSNRGF REVPIRAPAFVI	SEQ ID NO: 128
JM 128	MSRCSCWRIDVFRNSGKSSTVRTSVAVISFLGASRLGFGGVATLAGE LIASVYAAASDLTAIPWSLKATCMSESIRQYSAAGRSKLVPTVAC	SEQ ID NO: 129
JM 129	MVPTACAPMRSSSEDISPAVLVARSRDSMLSSFCFHASTVVFPPFTL RGASSSSACFSTFTSSVFLADTSRSCRRWAMVLCFSTSLSSTFNCCV WFW	SEQ ID NO: 130
JM 130	MGTGLRGALYRLLNGSTSGTHSRMGVRSPMPPRAWPRRWACRQKDSH WYVKHHRSEHRLKSGHPACLKPGPAWSIGPRCSSPWAVRTRTAGARW SFLALVLDRADQRWSGVGS	SEQ ID NO: 131
JM 131	MGLLTPILECVPDVEPFKSLYNAPRKPVPINTLPASLHPHDEQQVFL RQAQWLSYRFIPHEAARSSSPPLLVVIDPENLVTATYSSGGPANFES RPFYVMPGPYPTDWPKTLSVTSNTSVTHLSHDEICNLFTTLSREHGT VQGRDIFAAAPTNVTPERTANHPTWETENQLTTQTEPAEKTHVIPAS PKARTDPIAETTAHHSQGQASQHANNVNQPGQITSHASRNKPSTAPQ ASSRPEKLNTQTVPRLISQTSETAHINHPASGQVTEPKGIFGTYKPR	SEQ ID NO: 132

	VLTEPAKPAHASIASRQPEATTTVPKLPINAPTAKVFIGTASKFLPD VEESHGTTPGAHQSKIDQKQYGESQPHRTPHLEEVPRAPHVDTPTSA HINVPSSQGPKTIHARVTPGIQTVTPSAPPPAGQIRAFNTRFPEPTA GRSTTNRMWN	
JM 132	MLYFQEFGGVLVDESLRLDRMGRSIYSRPVRACETHFVFWAILLPHW LGSIPHPIRRGATGRRFWEACIECADLTGRWGGAGSYCLNTGCYARV YCFWTLARGDVYVCAGWSVDVRRPWNLFKVWGAVRLTFAVLFLIYL	SEQ ID NO: 133
JM 133	MSSLRVKEPIVQGRLEHDYPNHPLVAEMNNLPQGDMSPAQYAIAKRN YLVFLTAKHHYDMYTQKKNGILRKDHLRGLRGKKDASSSISSVLSGS GSAAPSVAPVASTLGSNSFTTISSGPHSLIGSIGPTPGGGPGSVAS SGIGSTSLSPSDATTLDTRRSSQNKKSK	SEQ ID NO: 134
JM 134	MPEDATLPGPPPPGVGPIEPINEWGPLEIVVKLFDPRVEATGATLGA AEPDPDKTLEILELASFLPRRPRRWSLRKIPFFFCVYMS	SEQ ID NO: 135
JM 135	MASGRLPDLAEDEAACHGRVPYPVHHWLDCSRLGLDFAASMRAIGLC PECYVCFVTYGLGAWEGQPPEWARTLISAPSFQTALNDIATGWMPDN PPKNGDVKSRLHDTGRLLLEAYAWVLRCICTGVGYADNEGLSLTAVP RGAWSRYLVVSFPRACCFVCKTLNCRQRFPLVTCSPQHALDLPVLRK KWNGAGCVAMQLNVPSISRRLGANLDERGLGPSDAGLLASLRELAPT VPCGNPFNALLRSLTFRGLLSMSRVVLPIGESTETEISRDLGQKVLA YNVLFPCISLPVWSQVVARSVLEKTVPAPRVVVCLECGYCLNFGRGK FETVNFPPTNVFFSRDQKEKQLSICATTGRVYCSYCGGSHMRVISLF EITCVGDPYLRCVLANNAAHSIRDANSLVSVVVPCLASPDCATGLLK HLRVAELFYLTSSISSLSCGKCNRS	SEQ ID NO: 136
JM 136	MGSTTRDMLNRPLNVRLLRRALNGLPHGTVGASSRSEASSPASEGPR PRSSRLAPKRLEMDGTFSCIATQPAPFHFFRKTGKSSACCGEHVTRG NRWRQLRVLHTKQHALGNDTTRYLDHAPLGTAVKLRPSLSA	SEQ ID NO: 137
JM 137	MSSGKRLVDELCDVVVSYLGPSGISLDLERCQDGAPVYAKGGAVPVC TVRLQHGCVYHLEFVYKFWLHKLERLAYPFAPCFVITNNGLATTLKC FLCKPRDADAQFGKNLPINSDVYLERNSSVFLGQDDFMKFKARLVFS GDLNVYSSMVICRTYFTEHRQVLQFLVVTPKSAKRLKTLLRTVFALT GHSDGLGALRRTGSVARPSGSELTDIGSGERCGNDRLTDSIGTIGGW PRGACLTWLKTKLPVMGAFLILSIIGWIVLGWA	SEQ ID NO: 138
JM 138	MMDRIRNAPMTGSFVFSQVRQAPRGHPPIVPMESVNRSLPHRSPLPI SVNSDPEGRATEPVRLNAPRPSECPVRAKTVLRRVFNRLALFGVTTK NCKTCRCSVK	SEQ ID NO: 139
JM 139	MSGDDLLAFESLLPEDMKIMFPTIYSRLNAINYCQYLKTFLCNRAQT RSAHCEHCMVLDAKVNAVKQVIHKIVSTDAVFTGAAHST	SEQ ID NO: 140
JM 140	MFVPWQLETLMKHWPSLRELVEQSFLPGTPDVAFNSPVLIHTQDSLQ PASSCRVCNILFTLVRTFPPPDSFFEDYGWLCLTCLYAPRSWTATLM VAADLLELIHMYFPQRVKDGPVYTTQNILGIDVQLHFFATRCFRPID REQILHTSHLNFLQTEFIRGMLEGTIPGSFCFKTSWPRTEKDDQQPT VACCSVGRGNHANRDNHLPDDLEEAFNSTNAKEKPSILGVFSATWSE SQLLGSDTQQATIHSQPSTFPTPEDADQSQGPCLMHPTLNLKTKNHT ASICVLCECLAAHPDAGPVLRDLRRDILENMENNVKLVNRISYILND PDSLSHVRDEHLRGLIKRCSAQEIHKHFFCDPLCVLNTYSHCPAVLF KCPPPEKYKKLKARLATGEFLDCNRIFDCETLQTLAVLFKGSQLAKI GKTTSLEIIRELGFQLRRHNIQITHPFQTSNLYI	SEQ ID NO: 141
JM 141	MYDMRLTSLTLFSMFSRMSRRRSLRTGPASGWAARHSHRTQMDAVWF FVLRLSVGCIRQGPCDWSASSGVGKVEGCEWIVACCVSEPRSWDSDH VAEKTPRMLGFSLAFVELNASSRSSGRWLSRLA	SEQ ID NO: 142
JM 142	MFDECPNDERDTHRPGAMVFRFNGNITDFEVHIGVPISLKKSTPSSW RRVRAEKNCVSETNFFHCIISLLQLPCLDAGCVDWGPSGRLTLGAYG VRDANRRLGCFGIV	SEQ ID NO: 143
JM 143	MPKQPRRRLASRTPYAPSVKRPDGPQSTQPASRHGSCKSEIMQWKKL VSDTQFFSALTRRHELGVDFLREMGTPICTSKSVMLPLNLKTIAPGR CVSLSSFGHSSNMGFNCSSCTPTDRSAVSLDANALGEDSARKNSELC SVALTFYHHAEKVVQHKGFYLSLLSHSMEVVRRSFTQPGLLYAHLVL KTFGHDPLPIFTVDANERLALWAVFHTRDLHLGETSLRLIMDNLPNY DITVDCIKQTYIMKFTPSRPDNATVTVPVNSICEAVATLDCTDEFRE	SEQ ID NO: 144

	EIQRGTTIINSQGSL	
JM 144	MLTRAPRLGASVQLTAVRLLLLFLTSSTPTAINCTKPGSVFFWLSWP KVFMENHYSFISVNSVSITVVAAGKISSRGKTATNC	SEQ ID NO: 145
JM 145	MWCLVQRAGPPVGCRSPGGVQVPRWGAGPPVGCRSPGGVQVPRWGAG PPVGCRSPGGVQVPRWGAGPPVGCRSPGGVQVPRWGAGPPVGCRSPG GVQVPRWGAGPPVGCRSPGGVQVPRWGAGPPVGCRSPGGVQVPRWGA GPPVGCRSPGGVQVPRWGAGPPVGCRSPGGVQVPRWGAGPPVGCRSP GGVQVPRWGAGPPVGCRSPGGAPGGSGWGGGSGWLRVGWRLRVAPGG VAAPGGSGWAQVLKATVNPTANPTQKSPCASRAEARLLTCASGALYI GQNTLPK	SEQ ID NO: 146
JM 146	MGNPRIDRSHSKHVGFTLFGESPLAGPNVPARCTWVLRNAKLPLPCR VPYSCSAIFEYTALHGWRAVGRWCANQKLMIHLLVLWLHNNTMLLIL GGCFGLYKGRRKHR	SEQ ID NO: 147
JM 147	MYSWGEFRTMERKMSLRVTRGSQKHITMGLFGAHKRAVGNGLGGAPA PPCARNLGRGVRRGSPKHVLMVAARTHRPLFGAGVIRRSAQNVAHGT HCTHGAHEGGGVAGRSHRAGRGARRLWHRASDVYGRNPLSRGIKGRR QGRFPLARRAVNQTDARRRLVVATVGFLLRCRVPSRDWLGDLSIKNA RRPLAQPPVNHGILAANWPKQTANPRVGFCLQVPLYYIYSIIFFPC	SEQ ID NO: 148
JM 148	MTPAPKSGRWVRAATIKTCFGDPRLTPRPKLRAHGGAGAPPSPFPTA RLWAPNRPMVICFCDPRVTRSDILRSMVLNSPHEYMFR	SEQ ID NO: 149
JM 149	MVPFGAHGAVFAARGRRRVTETCTHGANSGPWSAKCRSGSPEGHRNI SPWAYLVPISGPWEMGSVGRRRHHVPAIWGAGSGGGHRNMF	SEQ ID NO: 150
JM 150	MSCEHPPGYNGQESAGKTSTGLPVGEREARRYAACVSEVAPMGRMT TPATRRAAGADISQNRPRRQAARLPPPTTLILAFKLLFKARLFVARA	SEQ ID NO: 151
JM 151	MFPHKRIVDLGRHLEADDREAVLWLFDRPVSDNTPEGFANGLCPPTG EPGIPFPVLLEAVFLVGRLDLVSTFFLLDVGFIVERLRSSPSYFSPY KHLMLSINRQLSERDVKNLVFLTGNQLGRKRNQSPTFFQWISQMEKA ALVSPSDYLVLKDLLQAVSRRDVAKVVAANAPG	SEQ ID NO: 152
JM 152	MAFVGPVPTGTIDPVLYQDRALSNLLAHETSFVTSTACYGTVQTEVT LGMRVILGTWMRSVARAHQADASVFPLAVSILDRYLECRSIPRRRFQ RLGAACLFLAGKIRDLNPFKAAFLCFCAADDFSVADLLKQEKSVLKA LRWKLEAVLPTDAIGPALFKSGFTKEQLFALHSRVVESVHKAIVNPV TGGLSPSLVAAACALFSLGAAAPPLDKLAEAIGVSAATLTAAAESVA TTLRELDEDRILNNARGSS	SEQ ID NO: 153
JM 153	MWGSRQHRSGIVSGHGLRSSCRGHCGRRGGTREQAGGRSRGRGRGAA APASASAASASPTPPGPQVLVVVEQGHGSDTETATESGHGSSQGSPS GSGSESVIVLGSPTPSPSGSAPVLASDLSPRNTSGSSPGSPASHSPP PSPPSHPAPLSPAPPSSHHPSPDPQPPSFLQPLPHDSPEPPGPPTSS PPPNSPGPPQSPTPTSSPPPQSPPDSPGPQQSPTPQQAPSPNTQQAV SHTDHPAGPSRPGPPFPGHTSHTYTVGGWGPPRRPGGVPCLRLRCTS HNSHEDEVPERQREQEGEERQQQPARPPRPPRYPIPIPYPHPRRRYQ ENTAHKEDFIVRRWETGSTPLDRARGVTESSFVTQTPIHCIAWQGAY SFPGLEHPASAFCRTHLEVPSSRLFASRCSVKVAEPPRPSKKPVAGG NNFTHPPPTSMLA	SEQ ID NO: 154
JM 154	MGPVEALAIAVVQVSRAGIAEGARTLALAIVVVQVSWEGARTLEAQA VQVSRGATVAKTTEAADRAMDDATTAVQVRGGRGAMGVMVGANAMRG IPGTTLMCFEVTGLKLTPAQTRLAMALEIPTR	SEQ ID NO: 155
JM 155	MTDSDPDPEGDPCDDPCPDSVAVSVSDPCPCSTTTRTCGPGGVGEAE AADAEAGAAAPRPLPRLRPPACSLVPPRLPQCPLQELRNPCPDTMPE RCCRLPHMIAVYCV	SEQ ID NO: 156
JM 156	MRARPDQNSPPPSGHNRKRTKHRFCVRALRWLRVVERAIYLICRFLH AVNRDHVGQPATSFRHSIGTRVAKFLQGTLRKTRRH	SEQ ID NO: 157
JM 157	MALRVGGNLFEKDLLPPGVKHRHRPCVFNHVGRNYINAAAGDARHGS VRSSNALCGGPRALYRVPWVRVNNSPQRSYRYLAKTGIA	SEQ ID NO: 158
JM 158	MLGGITLTLLLATLATVRCALQTHYAAVPVHSTASLGCVLTTAHNVL IVTWQKQESPSPVNVATYSSEAGTVVQPPFAGRVDIPEHKLTRTTLK FFNATMEDEGCYLCIFNAFGVGKLSGTACLTVYVPLSMSVTFYPPIN PTQLVCRAEASPAPSVNWTGVPPELCSEPEVFPRPNGTTLVVGRCNV TSVDPEDLRNATCLVTHIGGLASARPLGPVFSDPLEGTSHYVVGVVA	SEQ ID NO: 159

	AVAVLGIFLTGVFLYRSM	
JM 159	MSDQARGVSEVFGIHRRYVAATHDQGCSVGSGKHFGFAAQLGWHAGP VNRRCGTGLGPTDKLRRVNWGVKRDGHGQGDVNRQAGGSRQLSHSKR VKDTQVAPLVLHSGIKKLQGCSGQLVFGDVNPTGERGLNHRARFGTI CGHVNGARRFLFLPGNDKNVVGCC	SEQ ID NO: 160
JM 160	MDALNNNLNLLMDFLSNYSNSYSSYDDNISYTLDTESTLCRLTIIFP PTIYAIICFFIFCITLLGNALVLYIFFKFKALANSVDVLMAGLCCNS LFLCASFLFSWLLYVAPQILTPATCKVEIFFFYLYTYFGVYIVVCIS LIRCLLVVFSRRPWVKHWASGFLCVCVSLIVALALSANASLYRTALR HPETSEWICYEDAGEDTVNWKLRIRTISAICGFLVPFGLLVLFYGLT WCIVKSTKLARKGAVRGVIVTVVVLFLIFCLPYHLCNFFDTLLRTGF VTETCYIRDVISVAMHICSLLQSMYSAFVPVVYSGLGSLFRRRVRDT WSMFRCFSTSGSL	SEQ ID NO: 161
JM 161	MAQRTNPRWAAAALSADEEAFIHDNSDAESVLALVPEQCFSEFLLWL VTRPSDNFDNDDDDPTLGVIWQLLAPLVNYAPLETRSAHLQGHHTIS LPYGPDLLRQPTTRSSELVQCLRDSGFDTALRLELARHLSCQTRRFV ADRVPPGTFAALTLGALVEYDVRVQRQLPVTVQSTAWRPLPERDPIC AAVMLPLQRNILPLAVQASNGNSYTVSRYAVMARRSYGCVFQRLPCE NVTHIADSFTHLHSAIRTGAGALQDILFHSTLLPGGDIRSALCGFYA TTPSVGAFSRARHRAINTTTTLHCQQLARTGTPVLGGFLKTVHSATT SEANVITTTSLLSCVPQAYTFLRRSLFNQPIICLGSFEPVDGDGNQR SLYLGSAAGINRINQTLSLAYEILEGPLFTSINRAHEPASTISHLGA LVSRGGLRLFVSQLPPTILSQLTATPDISRETVNDILLNKFLNVSAF VVFAVLPRDTEPEPGPLDAIRRAARICGCPFAVVGETCEEPGIQFVN DLELWNPGAWPIRQPTSAEVIATFGFDEQPVSSNWLVRPEEPEEGGE QAPSPTDWGLFRLASVVDQLLRCPTVGSKEFVTRHVDRCSNGLVAQQ CEVGPLGRPLSDYHIVNHTAVFTDRMARVPIHRPQPITRQDATERLG SPETWVTQGRGRLRWVGQCVAHGEQAYKMGIDAAVGARYAICEAVTN IMLAHVRRLSDITLTASVGWNPEEDQAWLLQHALFACKELCRDLSVN FAITSAGSTPCLSEELISATQQHQTVAPVPFNAVIITATAEVKSSRR RVTPDLKATGNLLVLVTFPGPHLTQGSTFEHLCLLPSPTLPDVQATH LANLFMLTESMLSRGLVVSGHDVSDGGVVVTAIEMALAGNRGLQICI PSEETPLPWLVSETPGVIFEILPQHVDEVRQACQNFDCQATVCGTVG QEGLSERIVISHNNEEVYSQTLTSVAANWTSFSDEQWYSWGPSFTPA QELYRKDYGCNRHNLGHLADVCRNSELTLFAVPSRPPAVAALIAPGA PLPRALMAAFTNVGFDVAAVSTNDLRGGNILRGFSGLTIGGNVGIED SYVGARCAIMGLLNDPGCYGGLMAFFRRADTFSLCCGEFGFQLLGAL GLLRETPHDTPGPKTPDQWDIHLEENASGNHECLWLNLHIPQTTISI MFRVLRGLVLPGWANGRYLGVRYPRDAIEYHLNQQQRIALNFHTGNP DPRMFAQHYPRNPSANSAVAAITSPDGRHLASLVDPAVVFHPWQWAY VPPELADMTISPWALAFQSLFLWCVRNRQ	SEQ ID NO: 162
JM 162	MRNHGSSQRPWVLWGPYGILPPSGYIFTVLRGVWVPAPGGARSTQRN PSRHARAQNPRPVGHPPGGERIREPRVPLAKPPHPPDHHQHNV	SEQ ID NO: 163
JM 163	MPTFPPMVKPENPRRMFPPLRSLVETAATSNPTLVNAAISALGSGAP GAIRAATAGGLDGTANSVSSLFLQTSARWPRLCRLHP	SEQ ID NO: 164
JM 164	MTILSDRPSWPTVPHTVAWQSKFWHAWRTSSTCWGRISKITPGVSDT SHGRGVSSDGMQICRPRLPARAISIAVTTTPPSLTSWPDTTRPRESI DSVSIKRLARCVA	SEQ ID NO: 165
JM 165	MAKFTLRSRHSSLQANSACCSSQAWSSSGFQPTDAVSVMSLRRRTCA SMMLVTASQMAYLAPTAASMPILYACSPWATHCPTHLSLPLPWVTQV SGLPRRSVASCLVIGWGRCMGTRAILSVNTAVWLTMW	SEQ ID NO: 166
JM 166	MPFCRRRGNLRRAGNPVRERPRAVEPGSVADQTADLGRSDRNFWVRR AARFLQLAGAPRRTGGGRRTGTLADRLGPIPPGLRGRSASAMSNRRQ QRVCHATCGQMLQRTRSSAVRSGTPGPTAVRLPHRQPHGGVYGQNGA GAHTSPPTDHQAGRDGTPG	SEQ ID NO: 167
JM 167	MFRCNGSITAAHIGSLSGNGLQAVDCTVTGSWRCTRTSYSTSAPSVR AANVPGGTRSATNRLVWQLRCLASSNRNAVSKPLSLRHCTSSLDLVV GWRSRSGP	SEQ ID NO: 168

JM 168	MFVSFATMGNTYDFYNNNIMEWTLQNYTLNTANIYSNGILWICMVKF TNKHCKNNWIVVCNICRYVAILLLFIINRGNIYEEINCLFFVTALIG MYAVTEASTTSSLTMALAYSIITANTGIF	SEQ ID NO: 169
JM 169	MACNCPFFVWCTWLFSNILTGTFWLISLAQYACDNNKDLYIVAVSTV ACFFFLWKSLGLYFYQSRSQRLNTPLLKLIPWITGMTL	SEQ ID NO: 170
JM 170	MPGGGRPASGAARRGLWGPGLGGRRGAAPPGSAGPGRSRESAGPGGA GPGGGPGPPRDPRPREPKAARRAARGGRGRRPRARAGRAEGREPGEA GGAPLGGPGAARETLAPGARWRPRPRAAAGRAPGGPRRAPPLGALAW RRC	SEQ ID NO: 171
JM 171	MPGGRRPAWRSSAGLPSPTSPRKVVSAPPGGGLGPGAPRRGRPRGAT EGPGRTGDRENARGGGGQRGTCACLWNTMACWPARLLGSLQACC	SEQ ID NO: 172

Several JMHV ORFs have been identified that can impact this model system.

For example, JM25 is homologous to collagen and myosin. Collagen is found in the arterial walls and during MS disease there is a break down of the blood brain barrier. Some forms of myosin are found in neurons and is involved in vesicular transport.

JM26 is homologous to myosin and sphingosine kinase. Some forms of myosin are found in neurons and is involved in vesicular transport. Sphingosine kinase is involved in cell cycle progression and is a major component of oligodendroglia. Oligodendroglia is the non-deural cfells of ectodermal orgin forming part of the advential structure (neuroglia) of the central nervous system; projections of the surface membrane of each of these cells (oligodendrocytes) fan out and coil around the axon of many neurons to form myelin sheaths in the white matter. With micorglia, they form the perineuronal satellites in the gray matter.

JM39 is homologous to succinate dehydrogenase. Succinate dehydrogenase is found in the mitochondria and is an enzyme of the oxidoreductase class that catalyzes the oxidation of succinate to fumarate, using a variety of hydrogen acceptors. Succinate dehydrogenase is down regulated in patients with multiple sclerosis.

JM41 shows homology to alpha-1a adrenergic receptor. Adrenergic receptors are involved in secreting epinephrine or related substances, particularly in sympathetic nerve fibers that liberate norepinephrine at a synapse when a nerve impulse passes.

JM48 shows homology to mucin. Mucin is defined as any group of proteins-containing glycoconjugates with high sialic acid or sulfated polysaccharide content. Lipmatosis is a condition characterized by abnormal localized or tumor-like,

accumulations of fat as well as an accumulation of mucin in the tissues. Lipomatous metaplastic changes occur with people diagnosed with multiple sclerosis.

  JM54 is homologous to collagen and myosin. Collagen is found in the arterial walls and during MS disease there is a break down of the blood brain barrier.

5 Some forms of myosin are found in neurons and is involved in vesicular transport.

  JM57 has homology to calcium channel proteins. Mitochondrial calcium membrane potential is a component of cellular survival. Once membrane potential is lost a cell will progress towards apoptosis.

  JM71 has homology to a chromatin associated protein. Chromatin is a

10 deoxyribonucleic acid attached to a protein structure base and is the carrier of the genes in inheritance. A characteristic of apoptosis is chromatin condensation and DNA fragmentation. Therefore, JM71 may have an anti-apoptotic function.

  JM76 has homology to plexin. Plexins have been shown to promote axon repulsion. Recent evidence has shown that if plexin expression is inhibited in

15 carcinoma cell migration and when it is overexpressed migration is inhibited.

  JM80 has homology to NADH-ubiquinone dehydrogenase. NADH-ubiquinone dehydrogenase is a protein involved in the mitochondrial electron transport chain. Generation of reactive oxygen species is a byproduct of this pathway and is important in the aging process and in neurodegenerative diseases.

20 JM85 has homology to a chromatin remodeling complex protein. Chromatin is a deoxyribonucleic acid attached to a protein structure base and is the carrier of the genes in inheritance. A characteristic of apoptosis is chromatin condensation and DNA fragmentation.

  JM87 has homology to mucin. Mucin is defined as any group of proteins-

25 containing glycoconjugates with high sialic acid or sulfated polysaccharide content. Lipmatosis is a condition characterized by abnormal localized or tumor-like, accumulations of fat as well as an accumulation of mucin in the tissues. Lipomatous metaplastic changes occur with people diagnosed with multiple sclerosis.

  JM88 has homology to neurexin. Neurexins link the pre- and postsynaptic

30 compartments of synapses by binding extracellularly to post-synaptic cell adhesion molecules and intracellularly to pre-synaptic PDZ domain proteins. These proteins are essential for Ca2+ triggered neurotransmitter release.

JM132 has homology to c-myc promoter binding protein. C-myc has been shown to be involved in cell proliferation and tumorgenesis.

JM152 has homology to cyclin D. Cyclin D is a key regulator of cell cycle. Cell cycle events that are regulated by cyclins play a major role in the loss of

5   neurons in diseases such as Alzheimer's disease.

JM166 has homology to collagen. Collagen is found in the arterial walls and during MS disease there is a break down of the blood brain barrierJM167 has homology to myosin phosphatase.   Some forms of myosin are found in neurons and is involved in vesicular transport.

10   JM168 has homology to a CC chemokine receptor. Recent evidence has shown CC chemokine receptor expression by mononuclear phagocytes in multiple sclerosis lesions.

Example 3

15   ## Non-human Primate Model for MS

MS is a devastating disease affecting an estimated 1 million people worldwide, or 0.1% of the U.S. population. Current research is directed at elucidating potential viral/bacterial causes of MS, as well as determining the involvement of the host immune system in the disease. Rhesus macaques have

20   provided a nonhuman primate experimental autoimmune encephalomyelitis (EAE) model of MS since the 1930's (Ferraro and Cazzull, *J. Neuropathol Exp. Neurol.* 7:235-260, 1948; Rivers, and Schwentker, *J. Exp. Med.* 61:689-705, 1935). Recently, the common marmoset has been used to develop an animal model for MS (Brok et al., *J Immunol* 165:1093-101, 2000; Genain and Hauser, *J Mol Med* 75:187-

25   97, 1997). The marmoset model relies on myelin oligodendrocyte glycoprotein-specific antibodies for demyelination (Genain et al., *Nat Med* 5:170-5, 1999; Genain et al., *J Clin Invest* 96:2966-74, 1995; Raine et al., *Ann Neurol* 46:144-60, 1999). While EAE studies have provided data into how anti-myelin T cells and antibodies can cause demyelination, there are questions about their relevance. Even more

30   important is that EAE induced in these animal models is due to active immunization with myelin antigens or passive transfer of myelin specific T cells, neither of which occurs in MS.

Until now there has not been a nonhuman primate model in which a naturally occurring chronic viral infection results in an MS-like demyelinating disease. The availability of the complete JMHV sequence, the ability to grow JMHV *in vitro* and the association of the virus with a demyelinating disease *in vivo* can be used in a

5   relevant nonhuman primate model for MS in the Japanese macaque.

It will be apparent that the precise details of the methods or compositions described may be varied or modified without departing from the spirit of the

10   described disclosure. We claim all such modifications and variations that fall within the scope and spirit of the claims below.